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Suspected Nonfatal Drug-Related Overdoses Among Youth in the US: 2016–2019

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Abstract

BACKGROUND AND OBJECTIVES: During the current drug overdose crisis, the United States is experiencing a significant number of overdose deaths, hospitalizations, and emergency department visits. Given the vulnerability of young persons to substance use, it is important to assess how this crisis affects the nation's youth. In this study, we investigate trends in suspected nonfatal drug-related overdoses (all-drugs, opioids, heroin, and stimulants) among youth using syndromic surveillance data from 2016 to 2019.

METHODS: A retrospective analysis of emergency department syndromic surveillance data were used to detect quarterly trends in suspected drug overdoses from April 2016 through September 2019 among youth aged 0 to 10, 11 to 14, and 15 to 24 years. Syndrome definitions were developed using chief complaint free-text and discharge diagnosis codes to identify overdoses involving all-drugs, opioids, heroin, and stimulants. Pearson χ^2 tests detected quarter-to-quarter changes, and joinpoint regression analysis assessed trends over time.

RESULTS: On average, there was a 2.0% increase for youth aged 0 to 10 years and a 2.3% increase for youth aged 11 to 14 years for suspected all-drug overdoses. Suspected heroin overdoses decreased by an average of 3.3% per quarter for youth aged 15 to 24 years. Among all age groups, suspected stimulant overdoses increased across the study period, 3.3% for 0 to 10-year-olds, 4.0% for 11- to 14-year-olds, and 2.3% for 15- to 24-year-olds.

CONCLUSIONS: Suspected stimulant-involved drug overdoses appear to be rising among youth. These findings could inform targeted interventions, such as stimulant-focused prevention,

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and comprehensive approaches, including school-based prevention and other strategies to lower morbidity and mortality.

Drug overdose deaths, hospitalizations, and emergency department (ED) visits have increased from the 1990s to 2018. 1-4 Although much of the focus of the drug overdose epidemic is on adults, ⁵ it is also important to investigate the effects on youth. Exposure to substance use in a child's home, a commonly identified adverse childhood experience, is associated with poorer outcomes as an adult compared with youth without this adverse childhood experience. 6 This experience could also increase the likelihood for misuse of prescription drugs by youth. 6 The accessibility of opioid analgesics and the concurrent increase in misuse of these medications may have contributed to an increased frequency of opioid overdoses among youth. ^{7,8} Use of illicit drugs and misuse of prescriptions drugs during youth can have lasting consequences into adulthood. For example, using drugs during youth can increase the risk for delinquency, academic underachievement, drug use disorder, teenage pregnancy, and depression. 9-14 Moreover, a maturing and developing brain is particularly vulnerable to the acute effects of drug use, and these effects may predispose youth for developing a substance use disorder as an adult. 15,16 Recent data from the Youth Risk Behavior Survey demonstrate that lifetime illicit drug use (eg, cocaine, heroin, methamphetamine) among 9th- to 12th-graders has decreased from 2009 to 2019. However, 11th- and 12th-graders had significantly higher rates than 9th- and 10th-graders, suggesting developmental effects.¹⁷

The literature on youth drug overdose is emerging. Gaither et al ¹⁸ found that from 1999 to 2016, the pediatric mortality rate from opioid poisonings increased by 268.2% (0.22 to 0.81 per 100 000 population), with 80% of these deaths classified as unintentional. In addition, children aged 4 years had the second-highest opioid-involved overdose death rate overall among the pediatric population, as well as the second-highest increase in opioid-involved overdose death rate. Although the 4 year age group is at increased risk for unintentional ingestion, ¹⁹ national self-report surveys show that most youth will participate in some form of substance use before they graduate high school. ^{20,21} Data from the 2018 National Survey on Drug Use and Health indicated that persons aged 18 to 25 years had the highest past-year prevalence of illicit drug use, including prescription drug misuse (38.7%) and opioid misuse (including heroin use and/or prescription pain reliever misuse) (5.6%). ²¹ Furthermore, although little is known about nonfatal heroin overdoses among youth, researchers of a recent study found that between 2015 and 2016, nonfatal psychostimulant (eg, amphetamine, MDMA) ED visits increased for 0- to 24 year-olds. ²²

Timely data are essential to track sudden increases in drug exposures to facilitate an appropriate, effective, and rapid public health response. ED syndromic surveillance data collected through the Centers for Disease Control and Prevention (CDC) National Syndromic Surveillance Program (NSSP) BioSense Platform are timely and fill the data gap needed to provide information for action, with data being available for analysis within 24 to 48 hours of the visit. This source allows for near real-time collection of chief complaint data and, in some cases, discharge diagnoses to track suspected drug overdoses, including all-drugs, opioids, heroin, and stimulants. ED syndromic data can track sudden increases in overdoses, allowing for a localized response. Research literature indicates increased

use of illicit drugs by developmental stage and increased opioid overdose deaths among youth, but little is known about current heroin or stimulant overdoses among this vulnerable population. The purpose with this study is to investigate trends in suspected youth nonfatal drug overdoses (ie, all-drugs, opioids, heroin, and stimulants) reported to EDs by using CDC NSSP data during 2016–2019.

METHODS

The CDC NSSP BioSense platform receives ED visit data on demographics, chief complaints, and diagnosis codes, including the standardized *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM), *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM), Systematized Nomenclature of Medicine Clinical Terms, and other procedural codes. Unstandardized, free-text chief complaint data are generally reported to NSSP within 24 to 48 hours of an ED visit, with discharge diagnosis codes coming a few days to several weeks later. Although ICD-9-CM transitioned to ICD-10-CM on October 1, 2015, the definitions for this study included both diagnosis code versions for those hospital systems that included ICD-9-CM codes in medical records. Data were presented quarterly from April 2016 to September 2019 and were defined as follows: January 1 to March 31 (quarter [Q] 1), April 1 to June 30 (Q2), July 1 to September 30 (Q3), and October 1 to December 31 (Q4).

NSSP coverage increased throughout the study period from ~54% of ED visits in the US in 2016 to ~70% of the ED visits in the United States in 2019.²³ Data were analyzed by using the Electronic Surveillance System for the Early Notification of Community-Based Epidemics software. Suspected all-drug, opioid, heroin, and stimulant overdoses were identified by using CDC-developed case definitions.²⁴ The all-drug category consisted of drugs encompassing the T36–T50 drug poisoning codes in ICD-10-CM and included, for example, over-the-counter medications, benzodiazepines, opioids, and stimulants; the opioid category included heroin, synthetic narcotics, and other unspecified narcotics; stimulants included drugs such as cocaine, amphetamines (eg, methamphetamine and ecstasy), and other psychostimulants. The all-drug syndrome definition included all other categories analyzed (ie, opioid, heroin, and stimulants). The heroin-specific syndrome definition included only heroin, whereas the opioid syndrome definition included heroin and all other opioids (eg, synthetic opioids like fentanyl).

The age groups for youth in this study were predetermined by the existing NSSP age categories and also aligned with CDC National Center for Health Statistics as 0 to 10, 11 to 14, and 15 to 24 years. For each quarter, proportions were calculated overall and for each age group by drug category per 10 000 ED visits. Linear change was calculated from Q2 2016 to Q3 2019. Quarter-to-quarter comparisons were conducted by using Pearson χ^2 tests in SAS version 9.4 (SAS Institute, Inc, Cary, NC) and a significance level of 1%. Average quarterly percent change (AQPC) for the overall time frame was calculated by drug category and for each age strata by drug category by using the National Cancer Institute's Joinpoint Regression Program (version 4.6).²⁵

RESULTS

Between April 1, 2016 and September 30, 2019, there were 89 536 857 ED visits for youth aged 0 to 24 years (n = 39 575 938 0 - 10 years; n = 9 330 693 11 - 14 years; n = 40 630 226 15 - 24 years) reported in NSSP.

Among children aged 0 to 10 years during this time period, there was an average of 22.3 suspected all-drug overdoses, 0.7 suspected opioid overdoses, and 0.6 suspected stimulant overdoses per 10 000 ED visits. Heroin overdoses were suppressed because of low frequency and unstable estimates.

Among children aged 11 to 14 years during this time period, there was an average of 43.2 suspected all-drug overdoses, 0.6 suspected opioid overdoses, and 0.7 suspected stimulant overdoses per 10 000 ED visits. Heroin overdoses were suppressed because of low frequency and unstable estimates.

Among adolescents aged 15 to 24 years during this time period, there was an average of 85.2 suspected all-drug overdoses, 13.2 suspected opioid overdoses, 6.95 suspected heroin overdoses, and 2.65 suspected stimulant overdoses per 10 000 ED visits.

For each of the 3 age cohorts, the AQPC across the study window was positive across quarters for suspected stimulant overdoses, with a 3.3% increase among 0- to 10-year-olds (SE = 0.01; P= .005), 4.0% increase among 11- to 14-year-olds (SE = 0.01; P< .001), and 2.3% increase among 15- to 24-year-olds (SE = 0.004; P< .001; Table 1). There was an average of a 2.0% increase (SE = 0.01, P= .03) among the 0 to 10 cohort and an average of a 2.3% increase (SE = 0.01, P= .001) for the 11 to 14 cohort among suspected all-drug overdoses. For the 15 to 24 cohort, suspected heroin overdoses decreased across the study window by 3.3% on average per quarter (SE = 0.004; P< .001).

We examined the data by quarters, and the percent changes between the last 2 quarters of data (ie, April to June 2019 and July to September 2019) revealed decreases among all 3 age cohorts for most of the substance categories (Fig 1). From Q2 2019 to Q3 2019, the rate of suspected all-drug overdoses among 0- to 10-year-olds fell by 8.6% (P<.01); among 11- to 14-year-olds, the rate of suspected all-drug overdoses among fell by 29.9% (P<.01); and among 15- to 24-year-olds, the rate of suspected heroin overdoses fell by 20.8% (P<.01).

DISCUSSION

Between April 1, 2016 and September 30, 2019, suspected nonfatal all-drug overdoses in 59 jurisdictions among 47 states increased for youth aged 0 to 10 and 11 to 14 years (2.0% and 2.3% AQPC, respectively). These visits tended to be a relatively rare occurrence among these 2 age groups, with an average per 10 000 ED visits of 22.3 suspected all-drug overdoses among youth aged 0 to 10 years and 43.2 suspected all-drug overdoses among those aged 11 to 14 years. Among 15- to 24-year-olds, the rate of suspected all-drug overdoses was over double the rate for 11- to 14 year-olds with an average of 85.2 suspected all-drug overdoses per 10 000 ED visits. Despite the rarity of these suspected overdoses and

given the age of these patients and the likely unintentional nature in many of these cases, efforts to halt these increasing trends are important.

We investigated by type of drug and found that suspected stimulant overdoses increased in each of the 3 age groups, with those age 11 to 14 years experiencing the largest AQPC increases (4.0%), followed by 0- to 10-year-olds (3.3%) and 15- to 24-year-olds (2.3%). This finding is consistent with a recent study in which authors that found that nonfatal ED visits for psychostimulant overdoses between 2015 and 2016 increased by 10.1% for those aged 0 to 14 years, 9.4% for 15- to 19-year-olds, and 9.9% for 19- to 24-year-olds. ²² The increasing trend in suspected stimulant overdoses could also reflect trends in fatality data, with stimulant deaths representing a growing proportion of drug overdose deaths in the United States, specifically among cocaine and psychostimulants deaths. ^{22,26}

According to current research, the most effective treatments for addiction to methamphetamine are multifaceted behavioral therapies that include such elements as individual counseling, family education, screening, 12-step support, and extracurricular activities. Pespite a lack of evidence-based treatments for stimulant-use disorder, there is a growing body of literature, with mixed results, examining whether medications that have traditionally been used to treat opioid use disorder (ie, buprenorphine and extended-release naltrexone) show promise for treating people who are dependent on stimulants. Although more research is needed on effective treatments for stimulant-use disorder, interventions need to account for treating not only adults, but also younger populations.

The third important finding in this study is that among adolescents age 15 to 24 years, suspected nonfatal heroin overdoses declined during the study period by 3.3% on average per quarter. From 2010 to 2015, deaths from heroin rose by 31.4% on average each year, and it was not until 2015 that deaths started to plateau. Moreover, this finding aligns with national heroin overdose death trends, which show a significant decline among 15 to 24 year-olds between 2016 and 2017. Youth must be given special consideration when evaluating the burden of drug overdose in the United States. Illicit drug use and prescription drug misuse tend to be the most prevalent among youth.

The recent literature on nonfatal drug overdoses in the pediatric population is limited, and although there are some researchers using self-report survey data to report on general substance use, few have explored overdoses among youth. Recently, data from both the National Electronic Injury Surveillance System (NEISS) and the National Poison Data System (NPDS) have been used by researchers to explore overdoses among this sample. NEISS serves to collect data on consumer product-related injuries in EDs in the United States. From 2004 to 2013, ED visits for unsupervised drug exposures among patients <6 years old increased by 5.7% annually, with opioid-related exposures accounting for 13.8% of total visits. However, a known limitation of NEISS is timeliness. NEISS does not use the standardized ICD-10-CM diagnosis codes and instead has their own unique set of codes extracted from medical records by trained coders. Although this may be a strength, it may be one of several reasons for slow data dissemination that limits the system's ability to inform rapid public health response.

Regarding NPDS, this system captures calls to poison control centers from medical professionals or the general public, usually seeking treatment advice. In 1 study using NPDS data, researchers found that between 2010 and 2014, >60% of opioid-related exposure calls for those <18 years were about children <5 years old. ³⁵ Among the 83 418 opioid-related exposure calls for those <18 years old, 73% were unintentional exposures. Another NPDS study looked at exposure calls related to psychoactive drugs among 10- to 18-year-olds and found significant increases in calls for methamphetamine and LSD from 2007 to 2017. ³⁶ As novel exposures become more frequent and recognizable and as recommended treatment protocols become more widely known, calls will likely decrease, limiting the effectiveness of NPDS as a surveillance system to monitor and track trends. The NEISS and NPDS data systems have strengths and weaknesses, but timely, reliable data are essential for this issue, which is why it was important to also use data from NSSP.

Over the past several years, drug overdoses contributed to a declining life expectancy in the United States^{37,38}; it is important not to overlook youth when forming overdose prevention strategies. More research is needed on effective long-term, evidence-based interventions to prevent and treat substance use disorders among youth; however, the most promising interventions involve a multifaceted approach. Interventions that include aspects of individual, school, family, and community coordinated care have shown promise at reducing or preventing substance use among youth.³⁹⁻⁴¹ Yet, substantial gaps in the evidence for youth-focused substance use interventions remain, especially among youth who may have already developed a substance use disorder. Effective strategies for adults with substance use disorder have rarely been replicated among young populations, and when researchers and clinicians have tried, findings are often mixed.⁴²

The current study supports interventions that occur in EDs after a suspected overdose. About a third of youth presenting to the ED with suspected overdose receive addiction treatment; the prevalence is even lower among youth who present with heroin overdose. As There are several ED- and primary care—based drug use prevention interventions to have shown promise among adult populations that could be adapted for youth. Furthermore, there have been successful ED- and primary care—based interventions that focus on youth for alcohol and cannabis prevention that could be adapted for other drugs. With the promise that these interventions have shown for drug use prevention for youth and young adults, and based on the findings from the current study, these drug use prevention interventions could be expanded to include other drugs in a developmental context. Additionally, there are opportunities for an upstream approach by modifying behavioral interventions that have shown promise for addressing opioid overdoses. For example, Wiese et al for increased focus on upstream interventions to combat the opioid crisis through educational programs for medical students, residents, and practicing health care providers. A similar approach could be applied for interventions to focus on prescription stimulants prevention.

In this study, we found that suspected stimulant overdoses are increasing across all ages, whereas suspected opioid overdoses were stable across the time period. Authors of a recent study highlighted large increases in deaths involving stimulants and synthetic opioids from 2016 to 2017.²² Although with the current study, we did not specifically investigate the use of multiple substances contributing to overdose, these findings together underscore the

importance of naloxone access, especially because the co-use of these substances heightens overdose risk.⁵¹ Prevention could include clinicians recommending and providing naloxone access to youth who misuse opioids or other illicit drugs, such as stimulants, that may unknowingly contain fentanyl.⁵² Additionally, research suggests that when practitioners prescribe opioids to youth, they should use the lowest effective daily dose, avoid prescribing opioids and benzodiazepines concurrently, and focus on prescribing short-acting opioids.⁵³

This study also highlights the need to prevent unintentional ingestion of substances in young children. Reducing ED visits for medication overdoses among young children is an objective of Healthy People 2020 (see Medical Product Safety 5.4).⁵⁴ Childproof packaging of prescription and over-the-counter medications can deter unintentional ingestion among children, ⁴⁹ but unintentional ingestions still occur when the medication is outside its normal storage location: for example, when the medication is on the counter because it is being taken by an adult, or an errant pill that fell on the floor. 55,56 Product reformulation and parent and caregiver education can be effective interventions for reducing unintentional ingestions; however, availability of medications in a house is a prominent risk factor for unintentional ingestion of opioids by children.⁵⁷⁻⁵⁹ The Food and Drug Administration Risk Evaluation and Mitigation Strategy requires that training be made available to all health providers involved with the management of patients with pain to decrease inappropriate prescribing and misuse of opioids, 60 which may reduce youth access to these drugs in their homes. There are fewer evidence-based prevention strategies for child unintentional illicit drug ingestion; those available are policy-based and primarily consist of criminally punishing parents or caregivers if children are exposed to illicit drugs. 61 Additional research into effective prevention strategies may reduce unintentional exposure to and ingestion of illicit drugs by children and adolescents.

Limitations

This study is not without limitations. One primary element of syndromic surveillance data are chief complaint text, which is recorded on the patient's admission into the ED and may not ultimately be reflected in the patient's final diagnosis. Consequently, we identify overdoses in this study as "suspected." Next, there may be suspected overdose events not captured in this study, such as overdose cases that are treated at urgent care facilities or at EDs that do not report into NSSP. Also, data completeness and facility coverage vary over time. NSSP coverage did increase over the study period, capturing 70% of all ED visits in the United States by the end of this study. To minimize the effect of facility coverage fluctuations, we use total ED visits as the denominator instead of total population estimates. Additionally, suspected overdoses in this study are not mutually exclusive to the specific drug type. For example, a patient may report to the ED for a suspected stimulant and heroin overdose and would therefore be included in all-drug, heroin, and stimulant categories. The unit of analysis in this study is ED visit, not patient; therefore, multiple visits by the same patient are possible. Furthermore, the case definitions may underestimate or overestimate suspected drug overdoses on the basis of coding differences in hospitals, the availability of discharge diagnosis codes, the transition of facilities from ICD-9-CM to ICD-10-CM coding, and the quality of chief complaint data. For these reasons, we do not report counts but rather percent changes. To further account for these reasons, we included ICD-9-CM,

ICD-10-CM, and Systematized Nomenclature of Medicine Clinical Terms codes in our case definitions. Next, future research could parse the case definitions into smaller and more granular drug types to identify specific overdose trends. In addition, we cannot determine for some cases whether the drugs used were illicit or prescribed drugs, and it should be noted that interventions could be tailored to route of drug procurement. Next, although we did not specifically investigate concurrent use of drugs and alcohol in this study, the interaction of alcohol and other drugs may result in increased toxicity of each substance, resulting in increased overdose risk. Researchers in future studies should investigate the concurrent use of alcohol and other substances among this critical population. In addition, a comprehensive study of cannabis-related ED visits is needed given the changing legislative landscape across the nation. Another limitation in this study is the authors' inability to modify the age categories. Given the potential developmental effects on behaviors, future researchers could investigate youth drug overdoses using more-nuanced age groupings. Last, findings are not generalizable to areas not participating in NSSP, and intent of overdose cannot be ascertained.

CONCLUSIONS

Although drug overdoses remain an infrequent event among youth, our findings indicate that all-drug overdoses are rising among youth <15 years of age; meanwhile, suspected heroin overdoses are declining among 15- to 24-year-olds. Although further research is needed to both indicate if these patterns are continuing and to identify the specific drugs driving the increases, our results suggest that targeted interventions, even with young children, such as multifaceted approaches including school, family, and medical providers may be warranted to prevent overdoses requiring medical treatment.

ABBREVIATIONS

AQPC average quarterly percent change

CDC Centers for Disease Control and Prevention

ED emergency department

ICD-10-CM International Classification of Diseases, 10th Revision, Clinical

Modification

ICD-9-CM International Classification of Diseases, Ninth Revision, Clinical

Modification

NEISS National Electronic Injury Surveillance System

NSSP National Syndromic Surveillance Program

Q quarter

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WHAT'S KNOWN ON THIS SUBJECT:

Nonmedical use of drugs during youth can have lasting consequences into adulthood. We know little about how youth have been affected from a nonfatal drug overdose perspective during the current drug crisis.

WHAT THIS STUDY ADDS:

In this analysis of emergency department syndromic data, we show that nonfatal overdoses increased for those <15 years of age, and suspected stimulant overdoses increased for all youth age groups. Suspected drug overdoses for youth are on the rise.

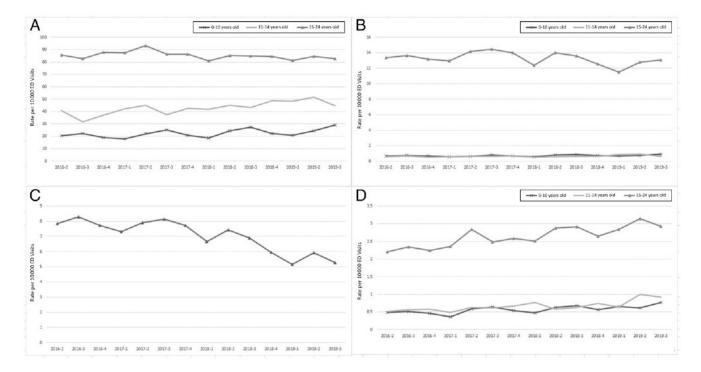


FIGURE 1. Trends in rates for suspected all-drug overdose (A), opioid overdose (B), heroin overdose (C), and stimulant overdose (D), by age group: 59 jurisdictions in 47 states, NSSP, April 2016 to September 2019. For (C), only the 15 to 24 age group is included because of suppression of small sample sizes.

TABLE 1

Percent Change in Quarterly Rates for Suspected All-Drug Overdose, Opioid Overdose, Heroin Overdose, and Stimulant Overdose, by Age Group-59 Jurisdictions in 47 States, NSSP, April 2016–September 2019

Characteristic	Q2 2016– Q3 2016	Q3 2016– Q4 2016	Q4 2016– Q1 2017	Q1 2017– Q2 2017	Q2 2017– Q3 2017	Q3 2017- Q4 2017	Q4 2017– Q1 2018	Q1 2018– Q2 2018	Q2 2018– Q3 2018	Q3 2018– Q4 2018	Q4 2018– Q1 2019	Q1 2019– Q2 2019	Q2 2019– Q3 2019	AQPC (95% CI)
0-10 y														
All-drug	13.8 ^a	1.6^{a}	0.7	6.5 ^a	11.7 ^a	6.9 _a	-2.6 ^a	7.2 ^a	5.84	-1.2	-0.7	6.4 ^a	-8.6 ^a	$2.0 (0.2 \text{ to} 3.8)^a$
Opioids	15.3	13.9	-11.1	-5.4	25.8	12.5	-17.8 ^a	20.5 ^a	3.6	5.2	4.1	6.0-	-7.8	1.5 (-0.5 to 3.5)
Heroin	I	1	1	l	I	I	I	I	I	I	I	I	1	I
Stimulants	8.3	8.9	-17.6	45.6 ^a	5.3	8.2	-1.8	6.0	2.3	1.1	23.9	-14.9	-5.2	3.3 (1.2 to 5.5) ^a
11–14 y														
All-drug	-14.8 ^a	24.0 ^a	24.5 ^a	-1.4	-15.6 ^a	30.5 ^a	6.7	-6.5 ^a	-7.3	20.4 ^a	11.3	1.84	-29.9 ^a	2.3 (1.0 to $3.6)^a$
Opioids	26.7	-21.1	26.7	0.0	5.3	22.5	-18.4	-5.0	7.9	4.9	53.5	6.1	-45.7	1.9 (-0.4 to 4.2)
Heroin	I	1			I	I	I		I	I	I	I	1	I
Stimulants	18.5	9.4	-8.6	18.8	0.0	23.7	29.8	-34.4	5.0	26.2	-3.8	49.0	-25.0	$4.0 (2.1 \text{ to} 5.9)^a$
15–24 y														
All-drug	6.8 ^a	7.2 ^a	3.9	6.6 ^a	0.0^{a}	5.0	-3.4^{a}	2.8 <i>a</i>	3.6	-3.2	-1.9	7.4 ^a	-13.1 ^a	-0.4 (-0.9 to 0.1)
Opioids	13.4	-2.6	2.3	9.6 _a	10.2	1.6	-8.8 <i>a</i>	10.3 ^a	1.2	-10.4^{a}	-6.2 ^a	14.2 ^a	-9.0	-0.6 (-1.5 to 0.2)
Heroin	16.7	-5.9	-1.2	8.2	11.2	-0.5	-11.3	8.8	-2.8	-16.5 ^a	-11.6	18.8 ^a	-20.8 ^a	-3.3 (-4.4 to $-2.1)^{a}$
Stimulants	17.5	-3.5	6.4	20.4 ^a	-5.3	8.7	0.4	11.8 ^a	5.6	-11.9	10.0	13.9	-17.0	2.3 (1.4 to $3.2)^a$

 3 Significant χ^2 test (P< .01) or a significant average quarter joinpoint (P< .01).