By Zirui Song

Mortality Quadrupled Among Opioid-Driven Hospitalizations, Notably Within Lower-Income And Disabled White Populations

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ABSTRACT Hospitals play an important role in caring for patients in the current opioid crisis, but data on the outcomes and composition of opioid-driven hospitalizations in the United States have been lacking. Nationally representative all-payer data for the period 1993–2014 from the National Inpatient Sample were used to compare the mortality rates and composition of hospitalizations with opioid-related primary diagnoses and those of hospitalizations for other drugs and for all other causes. Mortality among opioid-driven hospitalizations increased from 0.43 percent before 2000 to 2.02 percent in 2014, an average increase of 0.12 percentage points per year relative to the mortality of hospitalizations due to other drugs—which was unchanged. While the total volume of opioid-driven hospitalizations remained relatively stable, it shifted from diagnoses mostly involving opioid dependence or abuse to those centered on opioid or heroin poisoning (the latter have higher case fatality rates). After 2000, hospitalizations for opioid/heroin poisoning grew by 0.01 per 1,000 people per year, while hospitalizations for opioid dependence or abuse declined by 0.01 per 1,000 people per year. Patients admitted for opioid/heroin poisoning were more likely to be white, ages 50–64, Medicare beneficiaries with disabilities, and residents of lower-income areas. As the United States combats the opioid epidemic, efforts to help hospitals respond to the increasing severity of opioid intoxication are needed, especially in vulnerable populations.

The United States faces a growing opioid epidemic.[1,2] More than 64,000 drug overdose deaths were estimated to have occurred in 2016, including over 15,000 deaths from heroin and over 20,000 due to synthetic opioids.[3,4] Hospitals often serve as the last line of defense against substance use disorders, as overdose and intoxication frequently require care in an inpatient setting. Each day, about 7,000 people are treated in US emergency departments for opioid misuse.[5] Yet despite the burgeoning epidemic, little is known about the outcomes of patients hospitalized for opioid misuse. Moreover, data have been lacking on the demographic and socioeconomic characteristics of such patients, their intensity of opioid misuse, and the characteristics of their hospitalizations.

This study used nationally representative data on hospitalizations in the period 1993–2014 to examine the outcomes and characteristics of hospitalizations with opioid-related primary diagnoses, compared with hospitalizations due to other causes. It offers initial evidence on the trends in mortality rates, explained by examining the volume of hospitalizations and intensity of opioid misuse, and on the demographic

and socioeconomic characteristics of affected patients.

Study Data And Methods

DATA Data for the period 1993–2014 were gathered from the National Inpatient Sample of the Healthcare Cost and Utilization Project—the nation's largest all-payer inpatient database, which was developed by the Agency for Healthcare Research and Quality.[6] The database contains information for about eight million hospitalizations per year obtained from a stratified sample of US hospitals. Historically it included information about all discharges from approximately 20 percent of hospitals nationwide.[7] Beginning in 2012, it included information from about 20 percent of discharges from all participating hospitals, which improved the stability of the nationally representative estimates.[8] Sample weights produce national estimates. Data fields are standardized across hospitals, payers, and states. Annual estimates of the US resident population from the Census Bureau were used to standardize the volume of hospitalizations by population.[9]

Types of hospitalizations were defined using the *International Classification of Diseases*, Ninth Revision (ICD-9), diagnosis code in the primary diagnosis field. *Hospitalizations due to opioids* were defined as those in which the primary diagnosis field contained an ICD-9 code for nondependent opioid abuse, opioid dependence, opioid codependence with other substances, opioid poisoning, or poisoning by a specific opioid product such as methadone or heroin (for opioid-related ICD-9 diagnosis codes, see online Appendix A).[10] Validations for these codes, with a focus on the detection of opioid overdoses, have demonstrated a high positive predictive value and high specificity across different cohorts and areas of the country.[11–14]

Non-opioid hospitalizations were divided into two groups: those with a primary diagnosis due to other drugs (alcohol, cocaine, and other substances) and all hospitalizations with other primary diagnoses. Hospitalizations for other drugs were those with a primary diagnosis code in Major Diagnostic Categories 20 (alcohol or drug use or induced mental disorders) or 21 (injuries, poison, and toxic effect of drugs). Major Diagnostic Categories classify all diagnosis codes into twenty-five mutually exclusive categories and are used across payers (for the list of categories, see Appendix B).[10]

VARIABLES The key outcome variable of interest was in-hospital mortality. Secondary outcomes were hospital charges per day, hospital costs per day, and lengths-of-stay. Hospital charges excluded professional fees and noncovered services, and they were standardized by the data distributor by removing excessively high or low amounts. Hospital costs were calculated using the National Inpatient Sample cost-to-charge ratios, which were derived in a standardized manner.[15] Hospital charges and costs differ from the administratively set or negotiated fees that are reimbursed, but they provide a proxy for resource use that is comparable across hospitalizations. Length-of-stay, reported in days, typically reflected the number of midnights crossed during a hospitalization.

Patient characteristics included age, sex, race/ethnicity, primary payer, comorbidities, and quartile of median household income based on the patient's ZIP code of residence. Major racial/ethnic categories included white, black, and Hispanic. Major payer categories were Medicare, Medicaid, private insurance, and self-pay. Comorbidities were characterized using the Elixhauser Comorbidity Index.[16] While the use of a typical claims-based risk-adjustment model was not feasible in the absence of enrollment data, the Elixhauser index has been shown to outperform other standardized measures of comorbidity, such as the Charlson Comorbidity Index.[17–21] Hospital characteristics included size, urban or rural setting, teaching or nonteaching status, and region.

UNADJUSTED ANALYSIS Characteristics and outcomes of opioid-driven hospitalizations were compared to those of hospitalizations for other drugs and hospitalizations for all other causes. Differences were examined using the *t*-test, Wilcoxon-Mann-Whitney test for samples without assumed normal distributions, and the chi-square test for categorical variables.

The population-adjusted volume of hospitalizations (that is, the hospitalization rate) was calculated by dividing the nationally representative number of hospitalizations by the resident US population in each year. The volume of opioid-driven hospitalizations was decomposed according to type of opioid misuse—from opioid abuse and dependence to opioid and heroin poisoning. Hospitalizations for opioid and heroin poisoning were examined by age, sex, race/ethnicity, primary payer, and quartile of median household income.

ADJUSTED ANALYSES A linear multivariable model was used to evaluate changes in mortality among opioid-driven hospitalizations relative to hospitalizations for other drugs. With data aggregated to the annual level, the key independent variables included an indicator for the type of hospitalization, secular trend, and their interaction term—which captured differences in mortality trends among opioid-driven hospitaliza-

tions after accounting for mortality trends in hospitalizations for other drugs. In a segmented regression framework, the model further specified a secondary trend after 2000 to allow for differences in mortality trends after that time, given the increased availability of opioids that began at the turn of the century.[22–25] Additional independent variables included age, sex, race/ethnicity, payer, quartile of median household income, Elixhauser Comorbidity Index, procedures during the hospitalization, and month of admission.

Sensitivity analyses, including alterations in the covariates and the model, tested the robustness of main estimates. Additional sensitivity analyses included a segmented regression model at the hospitalization level with analogous independent variables, sample weights, and hospital fixed effects that accounted for time-invariant hospital factors. Standardized errors were clustered by hospital. Reported *p* values are two-tailed.

LIMITATIONS This study had several limitations. First, patient identifiers were excluded from the data for confidentiality. Thus, each observation was a distinct hospitalization, and readmissions were not identifiable.

Second, the sampling strategy in the National Inpatient Sample changed in 2012, as discussed above. However, the data continued to capture about 20 percent of hospitalizations nationwide.[8]

Third, hospital charges and costs are not synonymous with each other or with the actual amounts reimbursed by the payer, although they do make it possible to use billing as a proxy for resource use during hospitalizations in these data.[26]

Fourth, ICD-9 diagnosis codes, despite their validation in capturing opioid misuse, are likely to have some degree of subjectivity and measurement error. Nevertheless, the codes are the best instrument available in most administrative databases for identifying the cause of hospitalization. This study employed a conservative definition of the cause of hospitalization by using only the primary ICD-9 diagnosis code. While this narrowed the sample of hospitalizations that could be considered opioid related, it avoided contaminating the sample with hospitalizations for other indications in which an opioid-related code was used in a secondary diagnosis field. This approach differs from that of previous research that defined opioid-related hospitalizations using all diagnosis fields and that did not find an increase in mortality.[27] The focus on the primary diagnosis code is somewhat novel and not widely established. The specific code in the primary diagnosis field might also be influenced by awareness of the opioid epidemic among providers or changes in coding behavior. However, the primary diagnosis code is meant to reflect the clinician's judgment of the chief cause of admission, and thus it provides a meaningful lens through which to examine the reason for hospitalization in a more targeted manner.

Study Results

STUDY POPULATION For the period 1993–2014, the raw data in the National Inpatient Sample comprised 384,611 hospitalizations that were primarily opioid driven, 3,840,028 hospitalizations due to other drugs, and 159,265,806 hospitalizations due to all other causes. After sample weights were applied, the nationally representative sample was estimated to comprise 1,934,326 hospitalizations due to opioids, 19,220,610 due to other drugs, and 794,406,343 due to all other causes (for unweighted and weighted numbers of hospitalizations, see Appendix C).[10]

On average across the study period, patients with opioid-driven hospitalizations were younger (38.9 years) than patients hospitalized for other drugs (44.2 years) and for all other causes (47.6 years) (for patient and hospital characteristics, see Appendix D).[10] Similarly, relative to these two comparison groups, patients with opioid-driven hospitalizations were less likely to be white (53.8 percent versus 57.4 percent and 56.8 percent, respectively) and more likely to have Medicaid (40.1 percent versus 23.0 percent and 18.7 percent, respectively), be self-pay (uninsured) (17.2 percent versus 15.1 percent and 4.7 percent, respectively), and live in areas with the lowest quartile of median household income (32.3 percent versus 28.0 percent and 25.2 percent, respectively).

Opioid-driven hospitalizations were more likely than hospitalizations for other drugs or for all other causes to occur in urban teaching hospitals (50.4 percent versus 49.7 percent and 46.7 percent, respectively). Despite the fact that the largest numbers of hospitalizations in this data came from the South and Midwest, a disproportionately large share of opioid-driven hospitalizations occurred in the Northeast, relative to the shares of the two comparison groups of hospitalizations (43.9 percent versus 25.5 percent and 19.5 percent, respectively) (see Appendix D).[10]

CHANGES IN MORTALITY RATES The unadjusted in-hospital mortality rates for opioid-driven hospitalizations were relatively constant before 2000, averaging 0.43 percent (that is, 4.3 deaths per thousand admissions) (Exhibit 1). Between 2000 and 2007 the rates more than doubled (to 1.05 percent), and by 2014 they had nearly dou-

bled again (to 2.02 percent, or 20.2 deaths per thousand admissions). In contrast, mortality rates among hospitalizations due to other drugs remained stable throughout the study period, averaging 0.71 percent before and 0.75 percent after 2000. The mortality trend for all other hospitalizations in the United States steadily decreased throughout the period, from more than five times that for opioid-driven hospitalizations in 1993 to slightly below it by 2014.

The results of adjusted analyses showed that differences between mortality trends among hospitalizations due to opioids and those among hospitalizations due to other drugs remained constant before 2000 (a difference of −0.003 percentage points per year; $p = 0.75$). After 2000, however, mortality among hospitalizations due to opioids increased, on average, 0.12 percentage points (that is, 1.2 deaths per thousand) per year more than mortality among hospitalizations due to other drugs ($p < 0.001$). There was no significant change in mortality among hospitalizations due to other drugs ($p = 0.25$) during the study period. These adjusted mortality rates are visually displayed in Appendix E; the results of sensitivity analyses were consistent with those of the main analysis, as shown in Appendix F.[10]

DECOMPOSITION OF CHANGES IN MORTALITY Given that in-hospital mortality rates are the ratios of deaths (the numerator) to the volume of hospitalizations (the denominator), the rising mortality rates among opioid-driven hospitalizations could be explained by either a decrease in the volume of hospitalizations, an increase in the likelihood of death from opioid-driven hospitalizations (that is, the case fatality rate), or a combination of these factors.

The volume of hospitalizations in the United States due to opioids remained relatively constant during the study period, averaging 0.3 hospitalizations per thousand people (Appendix G).[10] Compared with hospitalizations due to other drugs, the average change was not significantly different (0.0004 hospitalizations per thousand per year; $p = 0.97$) (data not shown).

Within this stable volume of opioid-driven hospitalizations, however, an increasing share involved more intensive forms of opioid use. Hospitalizations for opioid dependence or abuse decreased, whereas hospitalizations for opioid poisoning—and, more recently, for heroin poisoning—increased (Exhibit 2). The results from adjusted analyses showed that hospitalizations for opioid dependence or abuse declined by 0.01 per thousand people per year ($p < 0.001$), while those for opioid and heroin poisoning collectively grew on average by 0.01 per thousand people per year ($p < 0.001$).

During the study period, the case fatality rate of hospitalizations for opioid dependence or abuse averaged 0.13 percent, whereas that for hospitalizations due to opioid poisoning and heroin poisoning averaged 2.86 percent (opioid poisoning: 2.30 percent; heroin poisoning: 4.87 percent) (Appendix H).[10] This gap remained fairly stable as the overall mortality rate of opioid-driven hospitalizations grew after 2000. The results from adjusted analyses showed that the case fatality rate for hospitalizations due to opioid and heroin poisoning grew by 0.006 percentage points per year ($p = 0.84$), relative to that for hospitalizations for opioid dependence or abuse (data not shown).

HOSPITALIZATIONS FOR OPIOID AND HEROIN POISONING The evolution of opioid-driven hospitalizations from opioid dependence or abuse toward opioid and heroin poisoning was not evenly distributed across demographic and socioeconomic dimensions. A decomposition of hospitalizations due to opioid and heroin poisoning (that is, those with a higher intensity of abuse) by age and sex demonstrated that for both men and women, those ages 50–64 accounted for the fastest-growing share of the hospitalizations during the study period (Appendix I).[10]

A decomposition of hospitalizations due to opioid and heroin poisoning by race showed that white patients accounted for the largest and fastest-growing share of hospitalizations in recent years (Exhibit 3). Analogously, a decomposition

In-hospital mortality rates among people hospitalized for opioid-related primary diagnoses and other primary diagnoses in the United States, 1993–2014
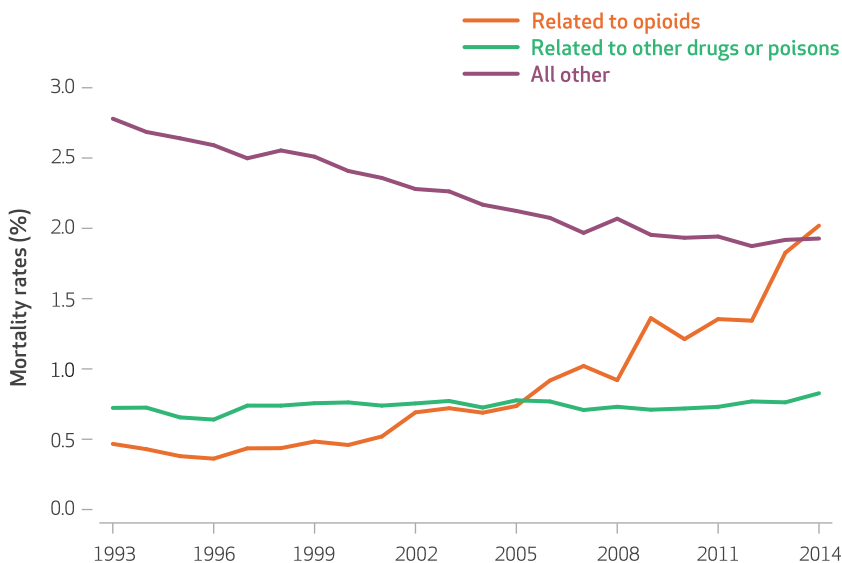
SOURCE Author's analysis of data from the Healthcare Cost and Utilization Project (see Note 6 in text). **NOTE** The categories of primary diagnoses are explained in the text.

EXHIBIT 2

Hospitalizations per 1,000 people in the United States for opioid-related primary diagnoses by type, 1993–2014
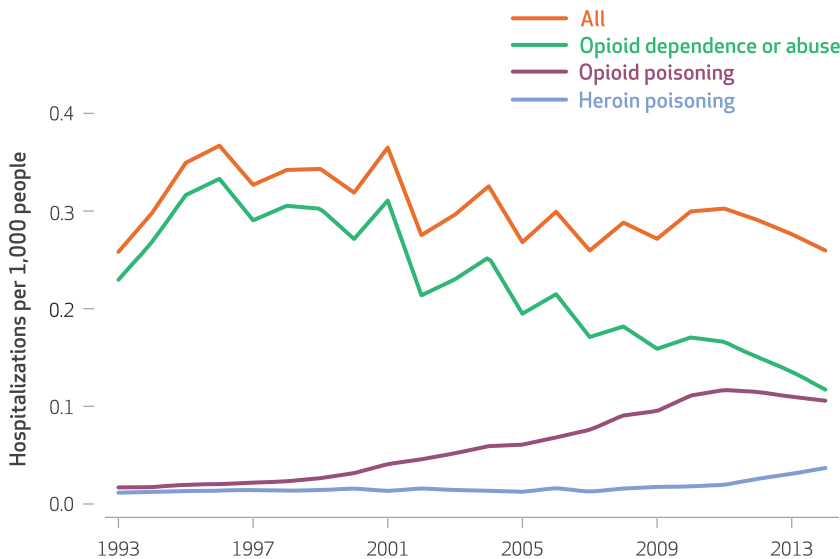
SOURCE Author's analysis of data from the Healthcare Cost and Utilization Project (see Note 6 in text) and the Census Bureau. NOTE The categories of primary diagnoses are explained in the text.

EXHIBIT 3

Hospitalizations in the United States for opioid and heroin poisoning by race/ethnicity, 1993–2014
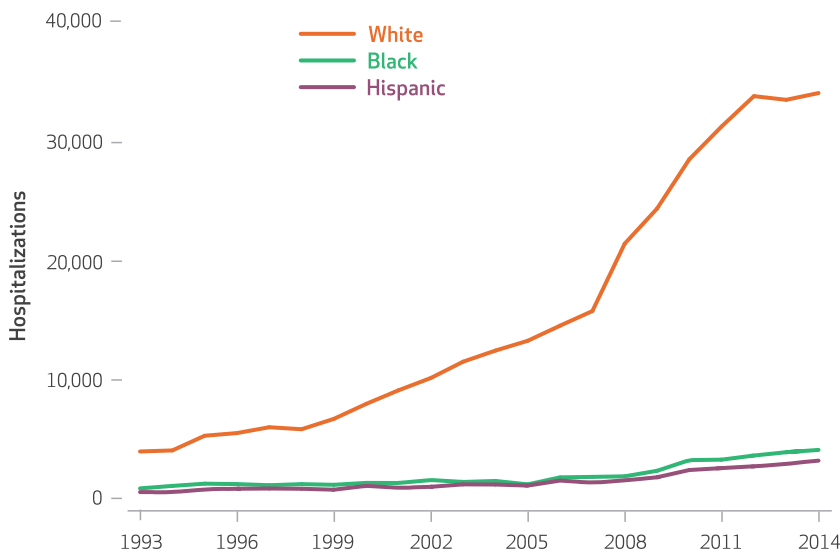
SOURCE Author's analysis of data from the Healthcare Cost and Utilization Project (see Note 6 in text). NOTE The numbers of hospitalizations are weighted to reflect nationally representative totals.

of these hospitalizations by quartile of median household income demonstrated that patients in the lowest quartile accounted for the largest and fastest-growing share (Appendix J).[10]

A decomposition of hospitalizations due to opioid and heroin poisoning by payer showed that people enrolled in Medicare, not those in Medicaid, accounted for the fastest-growing share. Medicare beneficiaries went from the smallest proportion of these hospitalizations in the 1990s to the largest share by the mid-2000s (Exhibit 4). Medicare beneficiaries hospitalized for opioid or heroin poisoning were, on average, 59.8 years old, which was younger than Medicare beneficiaries hospitalized for other drugs (63.6 years) and for all other indications (73.6 years). Overall, 59.3 percent of Medicare beneficiaries hospitalized for opioid or heroin poisoning were younger than age sixty-five, compared with 42.2 percent among beneficiaries hospitalized for other drugs and 15.6 percent among beneficiaries hospitalized for all other indications. Given that nearly all Medicare beneficiaries younger than age sixty-five receive Social Security Disability Insurance, most Medicare beneficiaries hospitalized for opioid or heroin poisoning were thus likely to have physical or mental disabilities.[28]

SECONDARY OUTCOMES While mortality among opioid-driven hospitalizations increased relative to mortality among hospitalizations for drugs and for other causes, indicators of resource use during opioid-driven hospitalizations did not demonstrate a significantly different rate of change relative to those of other hospitalizations (Appendix K1).[10] On average, after 2000, hospital charges per opioid-driven hospitalization increased $73 per hospitalization per year ($p = 0.74$) relative to hospitalizations for other drugs. Relative to hospitalizations for all other causes, charges per opioid-driven hospitalization decreased $68 per hospitalization per year ($p = 0.84$). These differential changes were similarly not significant when charges were converted to hospital costs.

Length-of-stay among opioid-driven hospitalizations increased, on average, 0.14 day per year ($p = 0.02$) after 2000, relative to that among hospitalizations for other drugs and 0.18 day per year ($p = 0.008$) relative to that of hospitalizations for all other causes (Appendix L).[10] Results from adjusted analyses that normalized hospital charges by length-of-stay showed that charges per day among opioid-driven hospitalizations did not change significantly relative to those for hospitalizations due to other drugs (a decline of $33; $p = 0.46$) or all other causes (a decline of $53; $p = 0.49$) (Appendix K2).[10]

Discussion

Mortality rates among opioid-driven hospitalizations have increased more than fourfold in recent years. This stands in stark contrast to the stable mortality rates for hospitalizations for other drugs and the decreasing mortality rates among all other hospitalizations in the United States.

Within the group of opioid-driven hospitalizations, as defined using the primary diagnosis code, the overall rate of hospitalizations changed little. However, the severity of these hospitalizations intensified, as hospitalizations for opioid dependence or abuse were replaced by those for opioid and heroin poisoning. Among patients hospitalized for opioid or heroin poisoning, the fastest-growing segments were people who were ages 50–64, white, and Medicare beneficiaries, and those who lived in areas with the lowest quartile of median household income.

The fact that Medicare beneficiaries—the majority of whom were younger than age sixty-five—accounted for the fastest-growing and largest share by payer of hospitalizations for opioid and heroin poisoning is consistent with increased opioid use among disabled Medicare beneficiaries. Nearly all beneficiaries younger than age sixty-five receive Social Security Disability Insurance, and over 40 percent of disabled beneficiaries use prescription opioids—with a growing proportion using opioids chronically.[29] The demographic makeup of the population hospitalized for opioids in these data reflects the burden of opioid morbidity and mortality nationally outside of the hospital setting.[30,31] These results are also consistent with broader trends in rising mortality rates in the United States due to poisonings: Relative to other developed nations, in the United States the increases are concentrated among middle-age, socioeconomically disadvantaged white populations.[32]

In recent years, data from the National Vital Statistics System have suggested that overall deaths in the United States due to opioid analgesics began to plateau in 2006.[33] Similarly, the Researched Abuse, Diversion, and Addiction-Related Surveillance System showed that diversion and abuse of prescription opioid medications plateaued or declined between 2011 and 2013.[34] Despite these encouraging developments, this study found that in-hospital mortality rates for opioid-driven hospitalizations defined by the primary diagnosis code have continued to climb in recent years. The fact that patients who are hospitalized may fare worse is consistent with the increasing severity of opioid abuse, especially among vulnerable and disabled populations.[35]

Hospitalizations in the United States for opioid and heroin poisoning by payer, 1993–2014
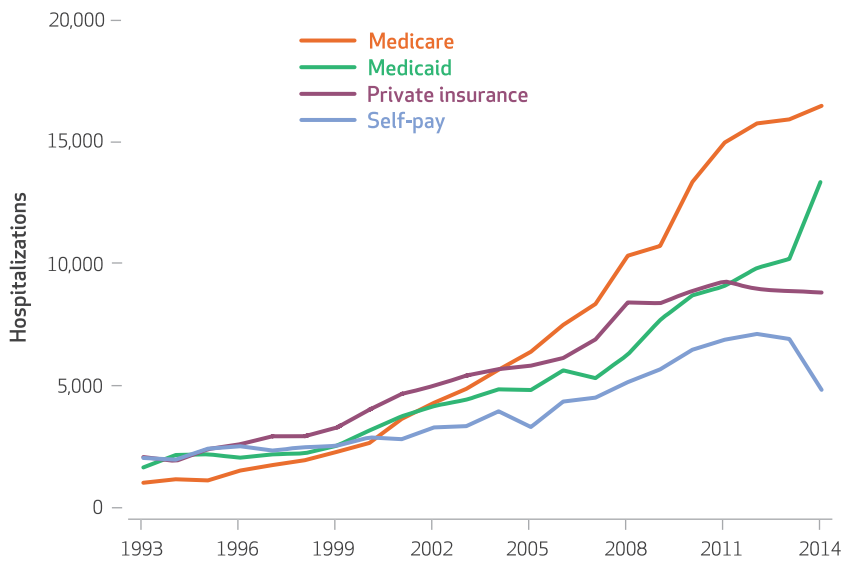
SOURCE Author's analysis of data from the Healthcare Cost and Utilization Project (see Note 6 in text). NOTE The numbers of hospitalizations are weighted to reflect nationally representative totals.

The detailed mechanisms behind these trends require further study. However, three potential mechanisms may help explain these descriptive findings. First, more potent opioids such as fentanyl, which can be 50–100 times as strong as heroin, have become increasingly available in the United States.[2,36,37] Second, the price of prescription opioids such as oxycodone has remained higher than or increased relative to the price of heroin, which has likely contributed to the substitution pattern seen here and more broadly nationwide.[38,39] Third, as the medical and public health communities respond to the opioid crisis, less severe cases of opioid poisoning may have been increasingly treated in the field, outpatient settings, or the emergency department, thus leaving a greater proportion of more severe cases for inpatient admission.

Conclusion

This is the first evaluation of nationally representative, multipayer data on the mortality rates and composition of opioid-driven hospitalizations in the United States, defined using the primary diagnosis code. Along with a growing literature, these findings resonate with the call for increased resources to help communities at risk. Policy makers have begun taking such steps.[40,41] The Department of Health and Human Services budgeted $94 million for federally qualified health centers to combat opioid use disorders.[42]

The Comprehensive Addiction and Recovery Act of 2016 and recent federal budgets have included additional funding.[43] As the nation moves forward in its effort to slow the opioid epidemic, such funding may have heterogeneous impacts across different populations. Notably, it can be especially challenging to implement effective interventions within disadvantaged populations. For instance, laws that restrict the prescribing and dispensing of opioids have not been associated with reduced opioid use or overdose among disabled Medicare beneficiaries.[44]

Until community-based efforts to tackle opioid misuse have taken root, treating opioid addiction and better equipping hospitals to care for patients with increasingly severe opioid abuse may help the health care system combat the rising mortality rates of patients hospitalized for opioid use disorders. ∎

NOTES

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10 To access the Appendix, click on the Details tab of the article online.

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