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Estimation of costs for emergency department and hospital inpatient care in patients with opioid abuse-related diagnoses

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Estimation of costs for emergency department and hospital inpatient care in patients with opioid abuse-related diagnoses

by

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Dedication

This work is dedicated to Ma, Pa, Ruchi, and Chaitanya – my pillars of strength.

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I would like to acknowledge the contributions of a few people in the completion of this effort. First and foremost, I would like to thank my advisor, Dr. Scott Strassels. He provided me with the right food for thought at the right time. I will forever be grateful and thankful to him. Truly, over the last two years, he has been my friend, philosopher, and guide. I would also like to thank my Committee members – Drs. Karen Rascati, Kenneth Lawson, and James Wilson. They have been supportive, encouraging, and patient.

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Abstract

Estimation of costs for emergency department and hospital inpatient care in patients with opioid abuse-related diagnoses

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The University of Texas at Austin, 2011

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The economic burden of prescription opioid abuse is believed to be substantial, however it is not known whether total and per-event hospital (ED and inpatient) costs associated with opioid abuse or misuse differ by insurance status. We also wanted identify predictors of charges.

We used the 2006, 2007, and 2008 files of the Healthcare Cost and Utilization Project's Nationwide Emergency Departments Sample (HCUP-NEDS) to identify events and charges assigned opioid abuse, dependence, or poisoning ICD-9-CM diagnosis codes (304.0X, 304.7X, 305.5X, 965.00, 965.02, 965.09). Using methods to account for the sampling design of the NEDS, we estimated national total and mean charges – overall and by insurance status (Medicare, Medicaid, private insurance, or self-payment). Charges were adjusted using the 2010 Medical Consumer Price Hospital Services index. We used a log-linked gamma regression model to assess potential predictors of charges.

The number of opioid abuse-related events was 515,896; 506,837; and 564,559 for 2006, 2007, and 2008, respectively. Approximately 55% visits in each year resulted in

inpatient admissions. Total charges billed for opioid abuse-related events were US$9.8; 9.6; and 9.5 billion for 2006, 2007, and 2008, respectively. Medicaid patients had the highest charges in each years followed by Medicare patients. Approximately 93% of total charges were due to subsequent inpatient admission. Overall unadjusted mean charges were $20,651; $20,373; and $18,384 for 2006, 2007, and 2008, respectively. Compared to events paid for by private insurance, Medicaid-covered events had significantly higher mean charges, and self-paid events had significantly lower charges ($p < 0.001$ for each year). Inpatient admissions resulted in significantly higher mean charges compared to treat-and-release ED visits ($p < 0.001$ for each year). We found similar results after adjusting for clinical and demographic factors. Age, number of diagnoses, inpatient admission, presence of cardiac tissue disorders, respiratory infections or failure, gastrointestinal hemorrhage, and acute pancreatitis were significantly positively associated with total charges billed ($p < 0.001$ for all).

This study helps in determining differences in hospital costs of opioid abusers by insurance status and in identifying potential predictors of such costs, resulting in better understanding the economic burden of opioid abuse on the healthcare system.

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CHAPTER 1

INTRODUCTION

Various reports document the growth and impact of prescription opioid abuse in the United States in the past decade. The National Survey on Drug Use and Health (NSDUH) data show that the number of Americans (12 years and older) reporting nonmedical use of prescription pain relievers in the past-year increased from 8.4 million in 2001 to 12.4 million in 2009. [1,2,3] An NSDUH report published in 2009 indicates that the proportion of 18-25 year old Americans reporting nonmedical use of prescription pain relievers rose significantly from 4.1% to 4.6% between 2002 and 2007; the increase in use reported by adults aged 26 or older during the same time period was 1.3% to 1.6%. [2] The 2009 NSDUH report also indicates that 2.2 million Americans aged 12 or older initiated nonmedical use of prescription pain relievers in the past-year, second only to the number of marijuana initiates (2.4 million); past-year dependence or abuse of pain relievers also increased from 1.5 million persons in 2002 to 1.9 million in 2009. [3]

Between 1998 and 2008, the proportion of admissions for substance abuse treatment reporting prescription pain reliever abuse increased more than four times; the increase for Americans aged 18 or older was approximately nine-fold. [4] The increase in pain reliever abuse was true for all age and racial/ethnic groups, for both genders, and for all education levels and employment categories.

In addition, emergency department (ED) visits related to opioid abuse or misuse increased by 66% from 2004 to 2007. [5] In absolute numbers, 286,521 ED visits in 2007 were attributable to opioid abuse. Another report indicates that ED visits involving nonmedical use of narcotic pain relievers increased by 111% between 2004 and 2008. [6]

Suicide attempts and overdose deaths involving opioids have also risen at a brisk rate. From 2005 to 2007, there was a 55% increase in ED visits for drug-related suicide attempts involving opioids; 16% of ED visits for drug-related suicide attempts in 2007 involved opioids. [5] Deaths due to unintentional overdose of opioids increased almost three-fold from 1999 to 2006. [7]

With the increasing nonmedical use of prescription opioids, it is imperative to assess the associated epidemiology and economic burden on the health care system.

LITERATURE REVIEW

EPIDEMIOLOGY OF NONMEDICAL USE OF OPIOID ANALGESICS

National estimates of prevalence and trends of opioid abuse and misuse

NSDUH is "an annual survey of the civilian, noninstitutionalized population of the United States aged 12 years old or older," sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA), a division of the US Department of Health and Human Services. [3] SAMHSA's Office of Applied Studies (OAS) releases annual NSDUH reports regarding the prevalence and incidence of the use of illicit drugs (including the nonmedical use of prescription pain relievers), alcohol, and tobacco products. Nonmedical use has been defined by SAMHSA as "use without a prescription of the individual's own or simply for the experience or feeling the drugs caused." Statistical information on substance dependence and abuse, as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), is also reported as part of periodic NSDUH reports.

The 2009 NSDUH report indicates that 12.4 million Americans aged 12 years or older used prescription pain relievers nonmedically in the past-year. Americans reporting nonmedical use of prescription pain relievers at least once in the past month numbered

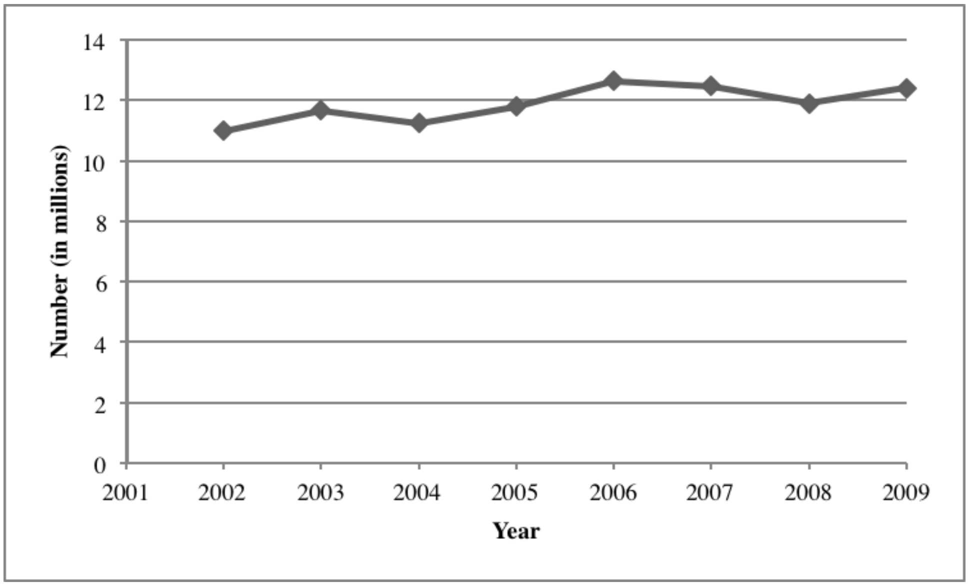
5.3 million; 1.4 million Americans reported being dependent on prescription pain relievers during the past-year, while the number of Americans abusing prescription analgesics was 459,000. [3]

Data from the 2009 NSDUH detailed tables provide estimates of the geographic and age group distribution of lifetime, past-year, and current nonmedical use of pain relievers. [8] The United States was divided into four regions for data collection as defined by the US Census Bureau: Northeast, Midwest, South, and West. Seven million Americans in the South (5.1% of the population of that region) reported using prescription pain relievers nonmedically in the past-year, whereas past-year prevalence in the Northeast, Midwest, and West was 2.1 million (4.4%), 2.5 million (4.6%), and 3.1 million (5.4%). Current nonmedical use of prescription pain relievers was highest in 18-25 year olds (1.6 million; 4.75%). Past-year prevalence of nonmedical use of pain relievers was 1.6 million (6.6%) in 12-17 year olds and 4.0 million (11.9%) in 18-25 year olds. Beyond 25 years of age, past-year prevalence gradually declined, with 159,000 Americans aged 65 or older (0.4%) using pain relievers nonmedically.

The relatively low prevalence of prescription pain reliever abuse in older adults can be misleading. A report from the Drug Abuse and Warning Network (DAWN) indicates that, in 2008, approximately one-third of ED visits in adults aged 50 and older involved nonmedical use of opioids. [9] Thus, despite the relatively low prevalence of nonmedical use of opioid analgesics in older adults, the proportion of ED visits in this age group attributable to abuse-related problems was high.

Data from 2002 to 2009 NSDUH detailed tables can be used to comment on the trend of nonmedical use, as well as dependence on, and abuse of prescription pain relievers. [8,10,11,12]

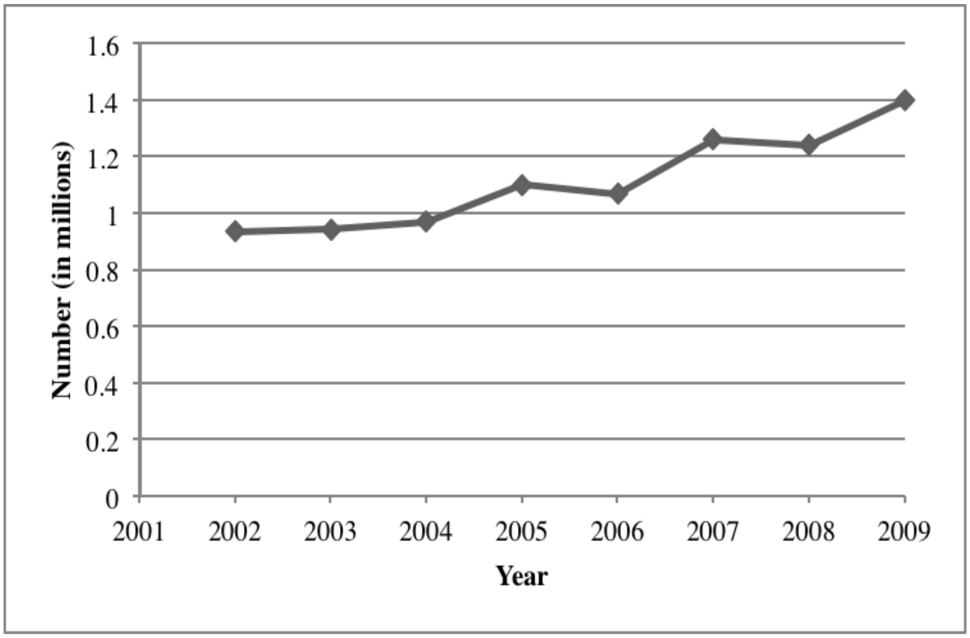
As can be seen from Figure 1, the number and proportion of Americans aged 12 years and older reporting past-year nonmedical use of prescription pain relievers has increased from 11 million in 2002 (4.7%) to 12.4 million (4.9%) in 2009.



Source: NSDUH data (2002-2009)

Figure 1: Past-year nonmedical use of prescription pain relievers in persons aged 12 or older: 2002-2009

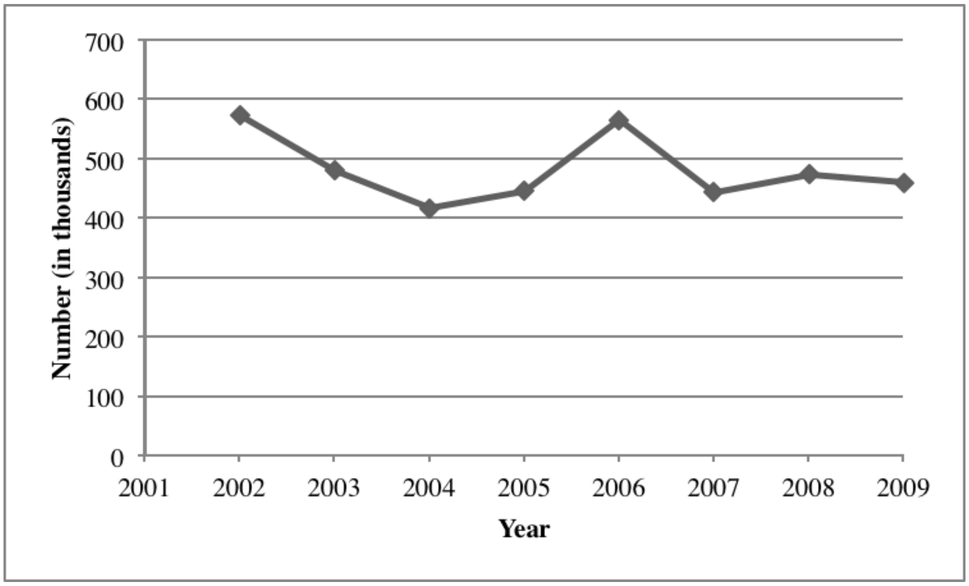
Figure 2 can be used to track the trend of prescription pain reliever dependence from 2002 to 2009. As can be noted, there has been a near-steady increase (number and proportion) in past-year pain reliever dependence in the population aged 12 years and older, from 936,000 people (0.4%) in 2002 to 1.4 million people (0.6%) in 2009.



Source: NSDUH data (2002-2009)

Figure 2: Past-year prescription pain reliever dependence in persons aged 12 or older: 2002-2009

Figure 3 indicates a decline in the number of people reporting past-year prescription pain reliever abuse from 2002 to 2003, after which the numbers remained fairly consistent (except in 2006). Even though there was a decrease in the absolute number (573,000 in 2002 to 480,000 in 2003), the proportion of the population reporting abuse of pain relievers remained constant (0.2%).



Source: NSDUH data (2002-2009)

Figure 3: Past-year abuse of prescription pain relievers in persons aged 12 or older: 2002-2009

The NSDUH also reports data on initiation of illicit drug use in the 12 months prior to the annual survey. According to the 2009 report, 2.2 million persons aged 12 or older initiated nonmedical use of prescription pain relievers in the past-year. The total number of first-time illicit drug users aged 12 or older was estimated at 3.1 million. Of these, 17.1% initiated illicit drug use with prescription pain relievers indicating a significant decrease in proportion from the 2008 survey (22.5%) but not significantly different from 2002 (proportion not reported). [3]

As was noted in the 'Introduction' section of this document, other measures of drug abuse (e.g., ED visits, deaths due to overdose) also indicate the increase in nonmedical use of opioid analgesics.

Relation between increased prescriptions and misuse of opioids

According to Katz et al., in 2002-03, a minimum of 431 million doses (4% of all opioid doses dispensed during the study period) were used nonmedically. [13] Increased legitimate use of a drug could lead to increased nonmedical use due to greater accessibility to the drug for diversion. [14] Some investigators have conducted studies to understand the association between use and misuse of opioids, and their trends over time.

Joranson et al. evaluated trends in use and abuse of opioid analgesics from 1990 to 1996. [15] The US Drug Enforcement Administration's Automation of Reports and Consolidated Orders System (ARCOS) database was used for medical use of opioids data, and DAWN ED mentions data were used to identify trends of opioid analgesic abuse. The investigators focused specifically on five opioids (fentanyl, hydromorphone, meperidine, morphine, and oxycodone) as these drugs were marketed as analgesics used to treat severe pain. Medical use of all 5 opioids increased over the study period, with increases ranging from 19% for hydromorphone to 1168% for fentanyl. Opioid analgesic abuse-related ED mentions increased 6.6% during the study period. However, ED mentions of all drugs (except morphine) under consideration decreased from 1990-1996; the decreases ranged from 15% for hydromorphone to 59% for fentanyl. Moreover, the proportion of opioid-related ED mentions to total drug abuse mentions decreased from 5.1% to 3.8%.

The taskforce on prescription opioid nonmedical use and abuse of the College on Problems of Drug Dependence (CPDD) conducted a study similar to the one done by Joranson et al. and got contrasting results. [14] They analyzed trends in use and abuse of five prescription opioids (morphine, fentanyl, oxycodone, hydromorphone, and hydrocodone) from 1994 to 2001. Additionally, the investigators also computed an "illicit use/licit use" ratio for all years under study. DAWN ED visits data were used as a measure of abuse while the number of prescriptions for opioid drugs was extracted from IMS Health, Inc. data.

The results indicated a concurrent increase in the availability of opioids and ED mentions. Absolute number of prescriptions and ED mentions of all drugs increased over the study interval. Oxycodone and hydrocodone were the two most prescribed drugs, with hydrocodone prescriptions being three times more than oxycodone for all years (39.2 million vs. 11.7 million in 1994, and 83.2 million vs. 26.5 million in 2001, respectively); these drugs also had the highest number of ED mentions (2001 figures: 21,567 for hydrocodone and 18,409 for oxycodone). The illicit use/licit use ratio for hydrocodone remained stable (0.24 in 1994 and 0.26 in 2001), while it increased dramatically for oxycodone, from 0.35 in 1994, 0.33 in 1999, to 0.46 in 2000, and 0.69 in 2001 (39% and 108% increases from 1999, respectively). Hydromorphone had the highest illicit use/licit use ratios ranging from 2.17 in 1994 to 2.49 in 1999 (ED visits data for 2000 and 2001 were not available), making it the opioid with the highest probability of abuse.

Novak et al. conducted a retrospective database study to determine trends in use and abuse of three opioid drugs with sustained-release dosage forms: morphine, fentanyl, and oxycodone. [16] The investigators used ED visits data from DAWN to analyze trends in opioid abuse, while the ARCOS database was used to identify trends in legitimate use; data from 1997-2001 were studied. Fentanyl, morphine, and oxycodone use increased 151.2%, 48.8%, and 347.9% respectively from 1997 to 2001. The percentage change decreased slightly on adjustment for equivalency (grams of morphine equivalents/100,000 population were calculated). During the same time period, DAWN ED mentions of opioid analgesics increased 83.5%; the increases for fentanyl, morphine, and oxycodone were 249.8%, 161.8%, and 267.3%, respectively. Opioid analgesic mentions in the DAWN database increased more than mentions for cocaine (19.8%), marijuana (70.8%), and heroin (31.6%) from 1997-2001. Even though a substantial increase in use and abuse of opioids was noted, opioid-related morbidity compared to all-drug abuse-related morbidity remains low. The proportion of total ED mentions in the DAWN database attributed to opioids as a class was 8.5% in 2001 compared to 16.6% for cocaine, and 9.5% for marijuana.

Gilson and colleagues used DAWN and ARCOS data to conduct an analysis similar to that of Novak et al. [16,17] The researchers evaluated trends in use and abuse of fentanyl, hydromorphone, meperidine, morphine, and oxycodone from 1997 to 2002. As was noted in the Novak study, increase in use of opioids co-occurred with a substantial increase in opioid abuse during the study interval, but opioid analgesics had the lowest number of mentions in the DAWN ED visits data compared to other drugs.

Using data from IMS Health, Inc. and DAWN, Dasgupta et al. computed correlations and coefficients of determination between use and abuse of opioids for the period 1994-2002. [18] A statistically significant positive correlation was found between ED mentions and prescribed morphine equivalent kilograms of opioid analgesics (r=0.99; $p<0.01$); a strong, linear, and positive association was observed (r^2=0.98). The investigators also found a statistically significant correlation between DAWN ED mentions and total number of kilograms prescribed during the study period for fentanyl, oxycodone, hydrocodone, morphine, methadone, and codeine ($p<0.01$ for all). The correlation coefficients remained statistically significant even after adjustment for potency (adjusted to morphine equivalent kilograms).

Thus, all studies investigating the association between use and misuse of opioids (except Joranson et al.) reported a sizeable concurrent increase over time in use as well as abuse of opioid analgesics. [14,15,16,17,18]

While the existing literature indicates a definite positive association between increased prescribing and misuse of opioids, other sources of abused opioids should not be ignored. Joranson et al. evaluated reports of theft or loss of controlled substances from 2000-2003 for six prescription opioids: fentanyl, hydromorphone, meperidine, methadone, morphine, and oxycodone. [19] The investigators found a substantial amount of prescription opioids being diverted from the distribution chain *before* being prescribed through thefts from pharmacies (89% of all thefts), manufacturers, physicians, distributors, and substance abuse treatment programs.

ECONOMIC IMPACT OF NONMEDICAL USE OF OPIOID ANALGESICS

The economic consequences of opioid abuse and misuse are thought to be substantial and have been well documented in various population groups. [20,21]

Societal costs associated with opioid abuse

Societal costs of drug abuse have been well studied over the last 40 years. [22,23,24,25,26] The studies have used varied data sources and methodologies to compute social costs. Two oft-cited studies are the ones by Rice et al. and Harwood et al. [25,26] Rice and colleagues estimated costs of alcohol and drug abuse, and mental illness, in 1985 and 1988. [25] Harwood et al. conducted a similar study and estimated costs for 1992. [26] Both studies reported estimates of healthcare, lost productivity, and abuse-related crime costs, but did not differentiate between prescription and non-prescription drugs, or licit and illicit drugs.

Rice et al. estimated costs of drug abuse at approximately $44.1 billion and $58.3 billion for 1985 and 1988, respectively (in 1985 and 1988 US dollars, respectively). [25] "Other related costs" accounted for the majority of costs associated with drug abuse in both years (74% and 78% in 1985 and 1988, respectively). "Other related costs" included direct costs of crime, motor vehicle accidents, destruction by fire, social welfare administration, and indirect costs due to incarceration, crime careers, and lost productivity of victims of crime as well as caregivers of abusers. Direct medical costs were estimated at $2 billion and $5 billion in 1985 and 1988, respectively.

Harwood et al. estimated societal costs of drug abuse at $9.9 billion in 1992. [26] This estimate included health care, lost productivity, crime, and social welfare administration costs. After a computerized search of the published, English-language literature, I found only two studies dealing with societal costs of opioid abuse. In 2006, Birnbaum et al. used Harwood's study to determine cost categories of drug abuse. [27] They used a prevalence-based estimation approach to determine costs of prescription opioid abuse from a societal perspective. The estimated costs included healthcare, workplace, and criminal justice costs. The data sources used were NSDUH, Treatment Episode Data Sets (TEDS), DAWN, and other government agencies. In addition, a claims database of privately insured employed individuals was used, which included medical and drug claims data for approximately 600,000 employed individuals from 1998 to 2001. Using multiple data sources creates difficulties in operationalizing definitions of drug abuse, dependence, and addiction. As a result, the investigators did not use a single definition of the above-mentioned terms, but rather multiple definitions as dictated by the various data sets. For the private insurance database, the investigators used ICD-9-CM diagnosis codes to identify opioid abuse patients. ICD-9-CM codes do not differentiate between prescription and nonprescription opioid abuse; the authors assumed that opioid abuse costs would not differ by opioid type and thus used these codes as a surrogate to select prescription opioid abuse patients. Cost estimates were calculated using either a quantity method (for excess medical costs, lost productivity due to premature death, and incarceration costs), or an apportionment method (for costs due to drug abuse treatment, criminal justice, lost/reduced wages, and incarceration).

Total societal costs of opioid abuse were estimated at $8.6 billion in 2001 US dollars ($9.5 billion in 2005 US dollars, $11.8 billion in 2009 US dollars). [27,28] Total workplace (lost productivity) costs were $4.6 billion (53%); these costs were attributed to reduced wages and employment, loss of productivity due to incarceration, or premature death of opioid abusers. Criminal justice costs accounted for approximately 17% of the total costs while total healthcare costs accounted for 30%. Of the $2.6 billion estimated as total healthcare costs, approximately $2.5 billion were attributed to excess medical costs of an opioid abuser (over and above the costs of a similar nonabuser), and the remaining $100 million was accounted for by the cost of treatment for opioid abuse. Excess medical costs were estimated using a log-linear regression model that controlled for demographics, employment status, location, insurance status, and certain comorbidities like cancer, arthritis, neuropathic pain and back pain. For privately insured persons, the per capita excess medical costs were $9,449 with the total for this group estimated at $802 million.

Since the investigators were using a database of privately insured individuals to determine excess medical costs of opioid abusers, they used indirect methods to estimate these costs for publicly insured and uninsured opioid abusers. The authors obtained a ratio of per capita Medicaid healthcare spending to that of spending for privately insured persons from the Centers for Medicare and Medicaid Services. This ratio was multiplied by the excess medical costs of a privately insured opioid abuser to determine the per-capita excess medical costs of publicly insured opioid abusers. The investigators then multiplied the per-capita value calculated by the number of publicly insured prescription opioid abusers (obtained from NSDUH and TEDS data) to obtain the total excess medical costs for this group. Thus, per capita excess medical costs for publicly insured individuals were estimated at $12,394 with total excess medical costs estimated at $894 million. The researchers did not take into account other sources of public insurance (for e.g., Medicare, CHAMPVA) while using this ratio; this might have resulted in an inaccurate estimate of medical costs. Similar calculations carried out for uninsured opioid abusers, using a ratio obtained from US Census Bureau publications, resulted in a total excess medical costs estimate of $785.6 million for this set of patients.

Birnbaum et al. expanded on the afore-mentioned study in 2010, by adding privately insured caregiver costs, opioid abuse prevention and research costs, cost of property lost due to crime, excess disability and medically-related absenteeism costs, as well as costs due to reduced productivity on-the-job, to the estimation of costs associated with opioid abuse. [28] Total societal costs were estimated at $55.7 billion (in 2009 US dollars). Of these, total health care costs were $24.9 billion (45% of total costs); total criminal justice costs were $5.1 billion (9%); and total lost/reduced workplace productivity costs were $25.6 billion (46%). Thus, the analyses indicated that reduced productivity due to opioid abuse is a more significant contributor to societal costs than had been previously thought. The higher cost estimate as compared to the previous study can be attributed to a greater number of categories of costs, as well as the time passed since the last study.

Direct costs associated with opioid abuse in privately insured individuals

White et al. conducted an analysis to estimate direct medical costs of opioid abuse from a private payer's perspective. [29] The investigators used a database that contained all pharmacy and medical claims for approximately two million privately insured employed persons (and dependents) from 1998-2002. The objective was to compare the average per-patient direct medical cost of patients with opioid abuse-related diagnoses (i.e., cost related to abuse as well as comorbidities) to cost for a control group of nonabusers. Patients between the ages of 12 and 64 years, and having at least one claim with opioid abuse-related ICD-9-CM codes between 1998 and 2002 were included in the analyses. The control group (nonabusers), matched by gender, age, employment status, and census geographic region, was identified to yield a controls:cases ratio of 3:1.

The prevalence of opioid abuse in the database varied from 5 per 10,000 privately insured individuals in 1998 to 8 per 10,000 in 2002. Fifty-eight percent of abusers had prescription claims for an opioid compared with 20% nonabusers. The average annual per-patient direct medical cost in 2003 U.S. dollars was $15,884 for opioid abusers compared to $1,830 for nonabusers ($p<0.01$); thus, the excess cost for opioid abusers was $14,054 annually. The authors conducted a sensitivity analysis by making two subgroups from the study sample based on ICD-9-CM codes. The average cost per-patient for an opioid "abuser" was $18,388 compared with $2,210 for the matched controls, and average cost for patients with an opioid "dependence" or "poisoning" diagnosis was $16,204 compared with $2,179 for the matched controls. Thus, the estimate of average direct medical costs for opioid abusers ranged from $15,884 to $18,388 versus $1,830 to $2,210 for nonabusers. Inpatient hospital cost was the largest proportion of medical costs for opioid abusers (46%; $7,239). For nonabusers, doctors' outpatient visits contributed the largest proportion (50%) to medical costs while inpatient hospital stays cost an average of $310 (17%) per nonabuser. The cost for opioid abusers was significantly higher than for nonabusers in all cost categories ($p<0.01$ for inpatient stays, outpatient visits, and drug costs; $p<0.05$ for other costs).

The investigators also found that opioid abusers used more medical services than nonabusers. Abusers were 12 times more likely to have an inpatient stay ($p<0.01$), and 4 times more likely to have an ED visit compared to nonabusers ($p<0.01$), and a significantly greater number of average outpatient visits than nonabusers (18.7 vs. 7; $p<0.01$).

Prevalence rates and risk ratios (rate for abusers vs. nonabusers) were computed for certain prespecified comorbidities. The investigators did not justify the prespecification of the comorbidities. Herpes simplex, burns, and non-A, B, C Hepatitis were the only comorbidities that did not have a significant risk ratio. Opioid abusers were approximately three times as likely as nonabusers to have a painful comorbidity (47.6% abusers vs. 17.3% nonabusers; $p<0.01$); the most prevalent painful comorbidity in abusers was low-back pain (19.3% patients). Comorbidities like nonopioid poisoning, Hepatitis (A, B, and C), psychiatric illness, and other substance abuse were 78.0, 36.0, 8.5, and 43.0 times as likely in opioid abusers as in nonabusers ($p<0.01$ for all). Opioid abusers were 6.0 times as likely as nonabusers to have a claim associated with vehicular traffic accidents. Even after controlling for comorbidities, opioid abusers were found to be 1.8 times as costly as a matched control group of depressed patients.

Direct costs associated with opioid abuse in Medicaid patients

McAdam-Marx et al. carried out a case-control study of the cost of opioid abuse in Medicaid patients. [30] Patients ≥12 years of age in the Medicaid Analytic eXtract (MAX) database who had at least one claim with opioid abuse-related ICD-9-CM codes, and 12 months continuous eligibility from 2002 to 2003, were selected and matched to Medicaid patients without any opioid abuse-related diagnosis (controls:cases = 3:1). The costs computed include inpatient, outpatient, long-term care (LTC), and prescription drug cost; costs of opioid abusers were compared with nonabusers.

The prevalence of opioid abuse in the database was 8.7 per 1000 Medicaid beneficiaries. Mean total cost (annual) for patients with an opioid abuse-related diagnosis was significantly higher compared to patients in the control group ($14,537 vs. $8,663; $p<0.001$). Opioid abuse patients had a significantly higher cost in all categories ($p<0.001$ for all) except LTC. Similar to the White et al. study, [27] the authors also calculated cost by diagnosis type (opioid abuse vs. dependence vs. poisoning) and found that patients with an opioid poisoning diagnosis had the highest excess cost compared to matched controls (excess cost=$9,886, $7,396, $5,777 for poisoning, abuse, and dependence, respectively; $p<0.001$ for all). Difference in cost by diagnosis type was more prominent when LTC costs were excluded.

Cost was also estimated with a two-step generalized linear model controlling for age, race, region, comorbidities, and poisoning. The total adjusted direct cost estimates for opioid abuse/dependence patients was $23,556 compared with $8,436 for the control group (difference = $15,120), the difference reduced to $12,794 once LTC costs were excluded.

The investigators reported the prevalence of comorbidities associated with opioid abuse in the Medicaid population. The method of selection of comorbidities reported was identical to that of White et al. [29] A considerable proportion (49%) of opioid abusers had a pain-related comorbidity and a similar proportion had psychiatric disorders. All comorbidities were statistically significant at $p<0.001$. Other substance abuse, psychiatric disorders, Hepatitis (A, B, and C), poisoning, and HIV/AIDS had risk ratios (prevalence of comorbidity in abusers relative to nonabusers) of 5.5, 1.9, 7.2, 7.7, and 4.7, respectively ($p<0.001$ for all).

Other cost studies

Ghate et al. noted that the studies by White et al. [29] and McAdam-Marx et al. [30] had similar designs, but cost comparisons are not reliable because of differences in reimbursement rates between private insurance and Medicaid. [31] The authors provided an insight into similarities and differences between the two studies as well as their limitations. Clinically undiagnosed opioid abusers were missed by both studies due to the use of ICD-9-CM diagnostic codes for patient identification. Additionally, cost estimates may be biased due to the various definitions of drug abuse, dependence, and addiction; [32] patients who were physically dependent on opioids may have been mistakenly diagnosed as opioid dependent. Ghate et al. fail to mention that another consequence of the varied definitions of abuse-related terms, patients with drug abuse may have been erroneously classified as drug dependent and vice-versa, which may have biased cost by diagnosis type (opioid abuse vs. dependence vs. poisoning) estimates.

A paper published in 2009 reports the potential cost savings from the development of an "abuse-deterrent opioid" or ADO. [33]The ADO was a tamper-resistant opioid formulation that was designed to be resistant to injection, snorting, chewing, and crushing.The investigators used information from the 2005 NSDUH survey, the ASI-MV® Connect drug surveillance system, and a private insurance claims database (n>6 million) to populate a budget impact model (BIM) and compute potential savings from a third-party payer perspective. The base-case analysis ("most-likely-case") indicated potential cost savings of $0.9 billion (in 2006 US dollars). The investigators also conducted sensitivity analyses; the "best case" scenario showed potential cost savings to be $1.6 billion while the "conservative" case estimated potential savings at $0.6 billion. Thus, the results indicate that introduction of a well designed ADO would result in sizeable cost savings in a privately insured population. A limitation of tamper-resistant opioids is that they can be ingested by other means, in copious amounts to counter the tamper-proof design.

Santora and colleagues used 1994-2002 data from a private hospital to evaluate direct medical costs per discharge (all values in 2002 US dollars) for admissions with an alcohol or drug abuse-related diagnosis. [34] ICD-9-CM codes were used for patient identification. Of the patients abusing alcohol or drugs, 11.8% abused only opioids. The number of admissions with opioid abuse-related diagnoses increased significantly from 1994-2002 (increase=196%; $p<0.001$). Total admission costs for patients abusing only opioids increased from \$1.7 million in 1994 to \$9.9 million in 2002 (increase=482%; $p<0.001$). The investigators also reported differences in abuse-related admissions by payer groups. An average of 9% of the admissions in the privately insured group abused opioids only, while the average proportion of patients in the Medicaid/Medicare and uninsured groups was 12% each. The number of opioid abuse-related admissions increased significantly over the study period in the privately insured ($p<0.001$) and Medicaid/Medicare groups ($p<0.001$). In contrast, admissions with an "opioids only" abuse diagnosis decreased significantly for patients who were uninsured ($p<0.001$). Hospital costs by payer type for patients abusing opioids only were not reported.

RATIONALE FOR PROPOSED STUDY AND IMPLICATIONS

As noted above, the economic burden of prescription opioid abuse is substantial and has been studied in a privately insured population as well as the Medicaid population; [27,28,29,30] generalizability to any population other than that included in the studies is limited. The US population is made up of privately insured, publicly insured (Medicaid, Medicare, Worker's Compensation, CHAMPUS, CHAMPVA, Title V, etc.), and uninsured individuals. A computerized review of the English language literature did not identify any studies of opioid abuse or dependence costs for the uninsured population. In addition, publicly insured patients, other than those insured by Medicaid, have also been neglected. As a result, the current study will contribute to addressing this gap, and to understanding if the health care costs of opioid abuse or dependence differ by insurance status.

For this analysis, we used the Healthcare Cost and Utilization Project-Nationwide Emergency Departments Sample [35] to calculate and compare costs from a healthcare system perspective. A significant (46%) part of the direct medical costs of privately insured opioid abusers are inpatient hospital stays, whereas for Medicaid patients, inpatient stays account for only 9% of direct medical costs. [27,28,29,30] This discrepancy is postulated to be because of inherent differences in the populations studied. [31] Determination of hospital costs (ED and inpatient) for opioid abusers in these and other insurance groups using a nationally representative database is likely to have significant health policy implications. Through this study, we endeavored to emphasize the importance of taking steps to reduce the growing prevalence of substance abuse and identify patient groups using most resources.

CHAPTER 2

SPECIFIC AIMS

1. To obtain a national estimate of total charges billed (estimate of cost) in the years 2006, 2007, and 2008, for privately insured, publicly insured, and uninsured patients with opioid abuse-related events, from a healthcare system perspective.
2. To obtain a national estimate of average (unadjusted) per-event charges for privately insured, publicly insured, and uninsured patients with opioid abuse-related events, from a healthcare system perspective.
3. To obtain a national estimate of average per-event charges (adjusted for demographic and clinical factors) for privately insured, publicly insured, and uninsured patients with opioid abuse-related events, from a healthcare system perspective, using regression modeling.
4. To identify factors associated with charges billed for opioid abuse-related events from the following: age, gender, location of residence of patient, US Census region in which hospital is located, primary payer for event, number of comorbidities, specific comorbidity type, patient's income, and discharge disposition, using regression modeling.
5. To compute the proportion of opioid abuse-related ED events for 2006, 2007, and 2008 by payer type.
6. To compute the proportion of opioid abuse-related inpatient admissions for 2006, 2007, and 2008 by payer type.
7. To describe the trends in opioid abuse-related total hospital charges billed, ED visits and, inpatient admissions from 2006-2008, categorized by payer type.

HYPOTHESES (FOR SPECIFIC AIM 4)

The following hypotheses will be tested (all hypotheses presented as null):

1. Age –

Null: There is no significant relationship between age and charges billed, holding all other factors constant.

2. Gender –

Null: There is no significant relationship between gender and charges billed, holding all other factors constant.

3. Urban-rural designation of patient's county of residence –

Null: There is no significant relationship between the urban/rural status of patient's county of residence and charges billed, holding all other factors constant.

4. US Census region in which hospital is located –

Null: There is no significant relationship between US Census region and charges billed, holding all other factors constant.

5. Primary payer –

Null: There is no significant relationship between primary payer and charges billed, holding all other factors constant.

6. Number of comorbidities –

Null: There is no significant relationship between number of comorbidities and charges billed, holding all other factors constant.

7. Presence of HIV infection –

Null: There is no significant relationship between HIV infection status and charges billed, holding all other factors constant.

8. Presence of hepatitis –

Null: There is no significant relationship between presence of hepatitis and charges billed, holding all other factors constant.

9. Presence of Herpes simplex infection –

Null: There is no significant relationship between presence of Herpes simplex infection and charges billed, holding all other factors constant.

10. Presence of neoplasm –

Null: There is no significant relationship between presence of neoplasia and charges billed, holding all other factors constant.

11. Presence of anxiety disorder –

Null: There is no significant relationship between presence of anxiety disorder and charges billed, holding all other factors constant.

12. Presence of bipolar disorder –

Null: There is no significant relationship between presence of bipolar disorder and charges billed, holding all other factors constant.

13. Presence of depression –

Null: There is no significant relationship between presence of depression and charges billed, holding all other factors constant.

14. Presence of schizophrenia –

Null: There is no significant relationship between presence of schizophrenia and charges billed, holding all other factors constant.

15. Presence of alcohol-related disorders –

Null: There is no significant relationship between presence of alcohol-related disorders and charges billed, holding all other factors constant.

16. Presence of suicide or self-inflicted injury –

Null: There is no significant relationship between presence of suicide or self-inflicted injury and charges billed, holding all other factors constant.

17. Presence of history of mental illness –

Null: There is no significant relationship between history of mental illness and charges billed, holding all other factors constant.

18. Presence of history of substance-related disorders –

Null: There is no significant relationship between history of substance-related disorders and charges billed, holding all other factors constant.

19. Presence of coma, stupor, or brain damage –

Null: There is no significant relationship between presence of coma, stupor, or brain damage and charges billed, holding all other factors constant.

20. Presence of cardiac tissue disorders –

Null: There is no significant relationship between presence of cardiac tissue disorders and charges billed, holding all other factors constant.

21. Presence of cerebrovascular disease –

Null: There is no significant relationship between presence of cerebrovascular disease and charges billed, holding all other factors constant.

22. Presence of respiratory infection –

Null: There is no significant relationship between presence of respiratory infection and charges billed, holding all other factors constant.

23. Presence of respiratory failure –

Null: There is no significant relationship between presence of respiratory failure and charges billed, holding all other factors constant.

24. Presence of liver disease –

Null: There is no significant relationship between presence of liver disease and charges billed, holding all other factors constant.

25. Presence of gastrointestinal hemorrhage –

Null: There is no significant relationship between presence of gastrointestinal hemorrhage and charges billed, holding all other factors constant.

26. Presence of acute pancreatitis –

Null: There is no significant relationship between presence of acute pancreatitis and charges billed, holding all other factors constant.

27. Presence of chronic pancreatitis –

Null: There is no significant relationship between presence of chronic pancreatitis and charges billed, holding all other factors constant.

28. Presence of skin and subcutaneous tissue infections –

Null: There is no significant relationship between presence of skin or subcutaneous tissue infections and charges billed, holding all other factors constant.

29. Presence of poisoning by psychotropic drugs –

Null: There is no significant relationship between presence of poisoning by psychotropic drugs and charges billed, holding all other factors constant.

30. Income quartile for ZIP code –

Null: There is no significant relationship between income quartile for ZIP code and charges billed, holding all other factors constant.

31. Discharge (from ED) disposition –

Null: There is no significant relationship between discharge disposition and charges billed, holding all other factors constant.

METHODS

DATA SOURCE

Healthcare Cost and Utilization Project (HCUP)

The Healthcare Cost and Utilization Project is a publicly available group of databases sponsored by the Agency for Healthcare Research and Quality (AHRQ). HCUP is the "largest collection of longitudinal hospital care data in the United States, with all-payer, encounter-level information beginning in 1988." [35] A new set of databases is released every year. HCUP databases consist of inpatient, ED, and ambulatory surgery data based on hospital billing records. Data regarding physician office visits, and pharmacy, laboratory, and radiology services are not included in the databases. HCUP data are sourced from non-federal community hospitals in the US; data from long-term care facilities, psychiatric hospitals, alcohol and chemical dependency hospitals, rehabilitation facilities, as well Department of Defense, Veterans Administration, and Indian Health Service hospitals are not included.

The HCUP group of databases consists of six databases – three state-level, and three national. The state-level databases are: the State Inpatient Databases (SID), the State Emergency Department Databases (SEDD), and the State Ambulatory Surgery Databases (SASD). The national level databases are: the Nationwide Inpatient Sample (NIS), the Nationwide Emergency Department Sample (NEDS), and the Kids' Inpatient Database (KID). HCUP is a State-Federal partnership. Most states report data for inclusion in HCUP. The state agencies that report data to HCUP for inclusion in the databases are known as HCUP Partners. All participating states do not report inpatient, ED, as well as ambulatory surgery discharge data. For example, in 2009, 43 states reported inpatient data, while 29 states provided ED data, and 28 states provided ambulatory surgery data.

Table 1: HCUP databases and their composition

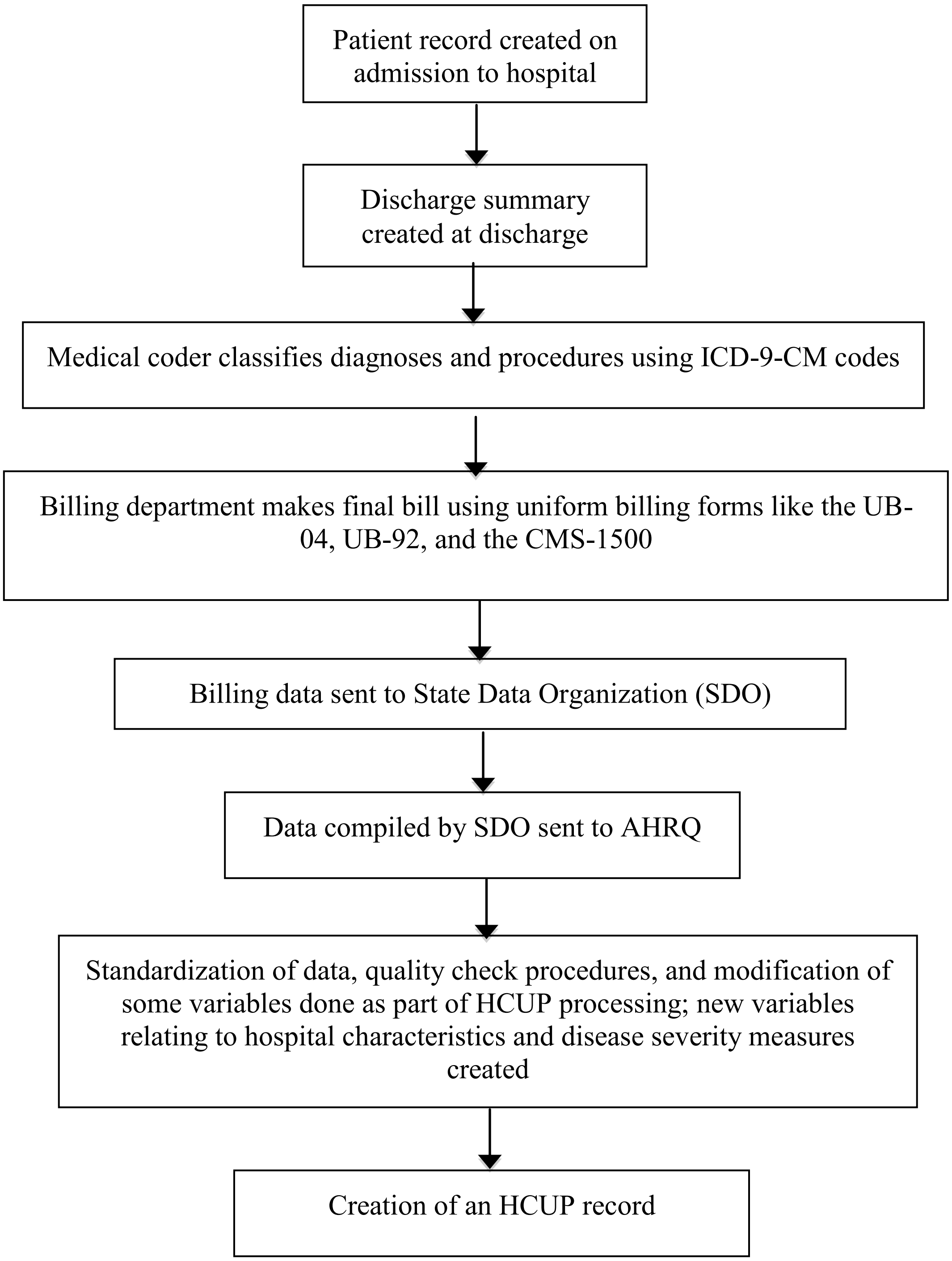
Database	**Data included**
State inpatient databases (SID)	All inpatient hospital discharges (including those inpatient admissions originating in the ED) from HCUP Partner states for a particular year
State Emergency Department Databases (SEDD)	All treat-and-release ED discharges from HCUP Partner states for a particular year
State Ambulatory Surgery Databases (SASD)	All ambulatory surgery discharges from participating states for a particular year
Nationwide Inpatient Sample (NIS)	All inpatient discharges from a stratified, random sample of hospitals from participating states for a particular year; stratification is done on hospital characteristic variables
Nationwide Emergency Department Sample (NEDS)	Treat-and-release ED visits as well as visits resulting in inpatient admission from a 20% stratified sample of hospital-based EDs for a particular year; stratification is done on hospital characteristic variables
Kids' Inpatient Database (KID)	Data from a systematic, random sample pediatric inpatient discharges, containing 10% of uncomplicated in-hospital births, 80% of complicated births, and pediatric non-birth inpatient discharges

Since the national databases are samples, they contain weighting variables for computation of national and regional estimates.

Creation of an HCUP record

The path of data from a patient record to one of the HCUP databases is illustrated in Figure 4. As can be seen from the figure, HCUP data is standardized to remove any differences between the data as reported by different states. HCUP also adds variables regarding hospital characteristics (e.g., US census region, urban/rural status, teaching status, ownership, bed size, and trauma center status), and severity measures (e.g., diagnosis-related groups and comorbidity measures). HCUP records all discharges from community hospitals in the US and is not a sample.

Figure 4: Path from patient record to uniform HCUP record



Nationwide Emergency Department Sample (NEDS)

HCUP-NEDS includes data from a 20 percent stratified national sample of hospital-based EDs and approximately 26 million ED visits from 950 hospitals (for 2006; these numbers are greater for 2007 and 2008). [36, 37, 38] It is the "largest all-payer ED database in the United States." [39] This database was created to examine ED utilization in the US. NEDS is populated with data from the SEDD (for treat-and-release visits as well as ED visits culminating in transfers to other hospitals), and SID (for all ED visits resulting in inpatient admission to the same hospital). These are event-level and not patient-level data (i.e., a patient visiting the ED multiple times in a year will have multiple records in the NEDS). Patients are not identifiable, and patient-level longitudinal analyses are not possible. Identification and selection of an ED record from the SID and SEDD for inclusion in the NEDS is based on certain HCUP criteria; at least one of the following needs to be true: [36,37,38]

- ED services indicated on discharge record with the help of revenue center codes 0450, 0451, 0452, 0456, and 0459;
- When revenue codes are not reported, ED charges recorded are greater than zero US dollars;
- ED physician services indicated on discharge record [Current Procedural Terminology® (CPT) codes 99281-99285]; or
- The admission source for an inpatient discharge is the ED

Some states impose restrictions on the release of certain data elements by HCUP. Such restrictions are usually enforced to protect the confidentiality of patients and hospitals in the HCUP databases. California, Georgia, and South Carolina place a restriction on reporting of external cause of injury codes (E codes), especially codes dealing with harm to patients during medical or surgical care. Iowa and Nebraska place restrictions on release of records of patients with an HIV diagnosis; Iowa also places restrictions on release of records of patients discharged after chemical dependency or psychiatric care. [36]

Sampling design

NEDS Universe –

Community, non-rehabilitation hospitals included in the American Hospital Association (AHA) Annual Survey Database and reporting total ED visits make up the universe for the NEDS. Non-rural hospitals reporting fewer than 10 ED visits in a year are excluded.

Sampling frame –

The NEDS sampling frame is made up of ED visits to community, non-rehabilitation hospitals in the states for which data is available, i.e., HCUP Partner States. The number of states reporting data to HCUP varies from year to year. Besides being included in the AHA data, it is necessary for hospitals in the sampling frame to have no more than 90% of their ED visits result in admission.

NEDS –

US Census region, urban/rural status, teaching status, ownership or control, and trauma center designation stratify the hospitals in the sampling frame. The state and the first three digits of the ZIP code are also used to stratify hospitals, albeit implicitly; this is done to make certain more precise geographic representation. The hospitals are sorted within each stratum by the first three digits of the ZIP code. Before random sampling from the stratum, hospitals within each three-digit ZIP code are randomized to minimize the probability of hospitals geographically close to each other within a state being picked in the random sample from the stratum.

After sorting, a random sample numbering 20 percent of the hospital-based EDs in the NEDS universe is taken from each stratum. All of the EDs from a stratum are included in the NEDS if the total number of EDs in the stratum is less than 20% of the universe. On the other hand, to protect confidentiality of hospitals, some strata have a sampling rate of greater than 20%.

The key variables of the NEDS include age, gender, income quartile for ZIP code, principal and secondary diagnoses, expected primary payer, total ED and total hospital charges, and discharge status from the ED. The NEDS also contains weighting data elements. Appropriate weighting enables computation of nationwide estimates of hospital services utilization and charges. The NEDS database is divided into four files:

- **Core file** – This file contains data for all the ED events from the sample of hospitals included in the NEDS.
- **Supplemental ED file** – This file contains data on procedures performed during ED visits that did not result in inpatient admission to the same hospital. Data to populate this file is sourced from the SEDD.
- **Supplemental inpatient file** – This file contains information and variables related to ED visits resulting in admission to the same hospital. Data for this file is sourced from the SID. Examples of data elements specific to this file include total charges for inpatient stay, and length of inpatient stay.
- **Hospital Weights file** – This is a hospital-level file and contains data elements for weighting of observations, and variance estimation.

The supplemental ED, supplemental inpatient, and hospital weights files contain data elements to provide linkage to the NEDS core file.

We used the NEDS database files from 2006, 2007, and 2008 for this project. The three years combined include data on hospital discharges that have taken place from January 1, 2006, to December 31, 2008. [40] Some differences exist in the data from year-to-year. The 2006 NEDS contains information on approximately 26 million ED visits at 955 hospital-based EDs. [36, 40] Twenty-four US states participated in the NEDS in 2006, representing 51.6% of the US population, and 48% of ED visits. [36] Five states (AZ, CA, HI, MA, and OH) did not report ED charge data. In 2007, three more states participated in the NEDS (NC, NY, and RI). [37, 40] The 2007 NEDS consist of data from 27 million ED visits and 966 hospitals. These states represented 61.3% of the US population, and 59.6% of ED visits. [37] Six of the 27 states (AZ, CA, HI, MA, NC, and OH) did not report ED charge data. Participation in the NEDS increased by one state (KY) in 2008, with data being reported from more than 28 million ED visits and 980 hospitals. [38, 40] The proportion of the US population accounted for by the participating states was 62.8%, while 61.3% of ED visits were represented. [38] Five of the 28 HCUP Partners (CA, HI, MA, NC, and OH) did not report ED charge data.

CASE SELECTION

Discharge records included in the analysis were selected using ICD-9-CM (*International Classification of Diseases, 9th Revision, Clinical Modification*) codes for opioid abuse, dependence, and poisoning (Table 2). [29] Over the years, there has been a considerable lack of clarity on the definitions of opioid abuse, dependence, and addiction. DSM-IV criteria for **substance dependence** include 3 or more of seven symptoms in a 12-month period: tolerance, withdrawal (physical dependence), impaired control, neglect of activities, great deal of time spent in substance-related activities, continuing use despite problems, and compulsion. DSM-IV criteria for **substance abuse** require that symptoms never meet criteria for dependence and one of 3 criteria are fulfilled in a 12-month period: use resulting in failure to fulfill duties at school, work, or home, recurrent use in situations in which use is physically hazardous (e.g., driving a vehicle, operating heavy machinery), or recurrent use despite social or interpersonal problems due to the effects of the substance. [41] NSDUH uses the DSM-IV criteria to define drug dependence and abuse. [3] The US Drug Enforcement Agency (DEA) distinguishes between drug dependence and addiction. [42] It describes **dependence** as the presence of physical dependence or craving, and that a person becomes dependent on a drug before getting addicted to it; **addiction** is physical as well mental dependence on the drug with social consequences due to drug-seeking behavior. The National Institute of Drug Abuse (NIDA) adopts a similar definition of addiction and specifically distinguishes it from physical dependence alone. [43]

The Liaison Committee on Pain and Addiction (LCPA) jointly formed by the American Pain Society (APS), American Academy of Pain Medicine (AAPM), and American Society of Addiction Medicine (ASAM) developed consensus definitions for addiction, physical dependence, and tolerance. [32] The Committee chose to use the term 'addiction' instead of 'dependence' for three reasons: a) so as to not create confusion between the terms 'dependence' and 'physical dependence'; b) to do away with the ambivalence of 'dependence' and the stigma attached to 'addiction'; and c) because, according to the committee, the term 'dependence' did not reflect "current understanding of the scientific basis of addiction." The LCPA defined **addiction** as, "a primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving."

Due to the various definitions of abuse, dependence, and addiction, all ICD-9-CM diagnosis codes related to opioid abuse were included in the study. Visits were identified as opioid abuse-related if they had principal or any secondary diagnoses (maximum number of diagnoses = 15) with at least one of the following codes: 304.0X, 304.7X, 305.5X, or 965.0X (except 965.01 – poisoning by heroin) (Table 2). The composite group of patients with the afore-mentioned diagnoses is subsequently referred to as "opioid abusers." To the best of our knowledge, there is no known way to separate prescription opioid abusers from non-prescription opioid abusers based on ICD-9-CM diagnosis codes; thus, the study sample is likely to contain prescription as well as non-prescription opioid abusers. Excluding ICD-9-CM code 965.01 (poisoning by heroin) will result in the closest possible estimate of prescription opioid abuse or dependence.

Table 2: ICD-9-CM codes and related diagnoses

Code	**Diagnoses**
304.0X	**Opioid type dependence**
304.00	- unspecified
304.01	- continuous
304.02	- episodic
304.03	- in remission
304.7X	**Combination of opioid type with any other**
304.70	- unspecified
304.71	- continuous
304.72	- episodic
304.73	- in remission
305.5X	**Opioid abuse (non-dependent)**
305.50	- unspecified
305.51	- continuous
305.52	- episodic
305.53	- in remission
965.0X	**Poisoning by opiates and related narcotics**
965.00	- opium (alkaloids), unspecified
965.01	- heroin (EXCLUDED)
965.02	- methadone
965.09	- other

ANALYSIS PLAN FOR SPECIFIC OBJECTIVES

Data management was done using SAS 9.1 (SAS Institute, Inc., Cary, NC, USA). Analyses were conducted using Stata SE 9.0 and 11.2 (StataCorp LP, College Station, TX, USA), taking the complex sampling design of the data into consideration. All charges were adjusted to 2010 US dollars using the Medical Consumer Price Index. Descriptive statistics (mean, standard errors, frequencies, and percentages) for all key variables were computed. All frequencies were reported as national estimates using the sampling weights given.

1. **To obtain a national estimate of total charges billed (estimate of cost) in the years 2006, 2007, and 2008, for privately insured, publicly insured, and uninsured patients with opioid abuse-related events, from a healthcare system perspective.**

   Total charges billed for each year by insurance group (public, private, and uninsured) were computed using the "svy: total" procedure.

2. **To obtain a national estimate of average (unadjusted) per-event charges for privately insured, publicly insured, and uninsured patients with opioid abuse-related events, from a healthcare system perspective.**

   Mean overall charges per event for each year by insurance group (public, private, and uninsured) were computed using the "svy: mean" procedure.

3. **To obtain a national estimate of average per-event charges (adjusted for demographic and clinical factors) for privately insured, publicly insured, and uninsured patients with opioid abuse-related diagnoses, from a healthcare system perspective, using regression modeling.**

   A generalized linear model (GLM) was developed to compute an estimate of the mean adjusted cost of opioid abusers. The independent variables used in the regression models were: age, gender, location of patient's county of residence, US Census region in which hospital is located, primary payer (Medicaid, Medicare, private insurance, self-pay, other payers – Worker's Compensation, CHAMPUS, CHAMPVA, Title V, other government payers), number of comorbidities, type of comorbidities, income quartile for ZIP code, discharge disposition (whether ED visit culminated in release, admission to same hospital as inpatient, transfer to other hospital, transfer to a healthcare facility other than a hospital, home health care, discharge against medical advice, death, or unknown disposition). Comorbidity variables required were created using AHRQ's Clinical Classification Software (2011). [44] This software groups ICD-9-CM diagnosis codes to create comorbidity variables. For example, 29 ICD-9 diagnosis codes can be used to identify various liver disorders; this software classifies any record having one of these diagnosis codes as having 'liver disease'. We used the "multi-level" classification system to generate variables. Use of this software helped classify comorbidities as organ system disorders and make the model more parsimonious (in contrast to using individual ICD-9-CM diagnosis codes to characterize comorbidities).

We used a gamma regression with a log link to estimate the outcome variable, i.e., charges billed, given the set of independent covariates. The appropriateness of the model was confirmed using the modified Park's test. This test was carried out by estimating a gamma regression model and then using the predicted values to compute residuals to use in the linear regression:

$$Log((y - \hat{y})^2) = g_0 + g_1(\log(\hat{y})) + \epsilon$$

where: y - outcome variable

$\hat{y}$ - predicted values of outcome variable

For a gamma distribution model to be appropriate, g_1 should be approximately 2. The g_1 estimates we obtained were 2.01, 1.99, and 1.94 for 2006, 2007, and 2008, respectively. We then used the predicted values to obtain national estimates of per-event adjusted mean charges, by insurance group.

The specific GLM used was –

$\text{Log}(E(Y|X)) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 + \beta_6 X_6 + \beta_7 X_7 + \beta_8 X_8 + \beta_9 X_9$,

with a gamma function, where:

$E(Y|X)$ is the expected predicted charges billed;

X_1 is age;

X_2 is gender;

X_3 is location of patient's county of residence (metropolitan, micropolitan, etc.);

X_4 is location of hospital (US Census region);

X_5 is primary payer (Medicare, Medicaid, private insurance, etc.);

X_6 is number of comorbidities;

X_7 is specific comorbidity group (groups like liver disease, heart disease, etc. were dummy coded as yes/no and introduced in the model as separate variables);

X_8 is income quartile for ZIP code;

and X_9 is discharge disposition.

The model was estimated using the "svy: glm" procedure.

4. **To identify factors associated with charges billed for opioid abuse-related events from the following: age, gender, urban location of hospital, US Census region in which hospital is located, primary payer for event, number of comorbidities, specific comorbidity type, patient's income, and discharge disposition, using regression modeling.**

   The regression model described for the previous objective was used to identify associations between the independent variables and the dependent variable. Estimates with a p-value less than 0.01 were considered statistically significant.

5. **To compute the proportion of opioid abuse-related ED events for 2006, 2007, and 2008 by payer type.**

Frequencies and percentages were computed using the “svy: proportion” procedure.

6. **To compute proportion of opioid abuse-related inpatient admissions for 2006, 2007, and 2008 by payer type.**

   Frequencies and percentages were computed using the “svy: proportion” procedure.

7. **To describe the trend in opioid abuse-related total hospital charges billed, ED visits, and inpatient admissions from 2006-2008, categorized by payer type.**

   Graphs were constructed to demonstrate the trends of total opioid abuse-related hospital charges, ED visits, and inpatient admissions from 2006-2008, by payer type.

CHAPTER 3

RESULTS

Descriptive statistics

The descriptive characteristics of the patient population are shown in Table 3. All descriptive statistics are national estimates using weights provided in the data. The average age for all three years is approximately 40 years, and is comprised of 55% male patients. The data show a similar distribution of patients by income quartile for ZIP code in all three years with approximately 33% of all patients in the first quartile, followed by approximately 25%, 20%, and 18% falling in the second, third, and fourth quartiles, respectively. In all three years, each event was associated with approximately seven ICD-9-CM diagnosis codes. Approximately 32% of the emergency rooms were located in Northeastern USA, with another 32% in the South, 18% in the Midwest, and 18% in the West.

Table 3. Descriptive characteristics of patients with opioid abuse-related ED visits

Variable[a]	2006		2007		2008	
	Mean (S.E.)	Frequency (%)[b]	Mean (S.E.)	Frequency (%)[b]	Mean (S.E.)	Frequency (%)[b]
Age	39.9 (0.24)	-	40.87 (0.23)	-	40.30 (0.28)	-
Sex						
- Male	-	285,840 (55%)	-	284,830 (56%)	-	314,818 (56%)
- Female	-	230,032 (45%)	-	221,958 (44%)	-	249,687 (44%)
Number of diagnoses	6.39 (0.14)	-	6.71 (0.11)	-	6.97 (0.14)	-
Income quartile for ZIP code						
- 0-25th percentile	-	172,781 (33%)	-	169,787 (33%)	-	161,262 (29%)
- 26th-50th percentile	-	126,130 (24%)	-	116,113 (23%)	-	144,653 (26%)
- 51st-75th percentile	-	111,943 (22%)	-	106,216 (21%)	-	114,758 (20%)
- 76th-100th percentile	-	88,989 (17%)	-	87,405 (17%)	-	101,396 (18%)
US Census region (of hospital)						
- Northeast	-	172,389 (33%)	-	163,879 (32%)	-	159,642 (28%)
- Midwest	-	82,515 (16%)	-	89,454 (18%)	-	104,505 (19%)
- South	-	164,871 (32%)	-	159,705 (32%)	-	188,579 (33%)
- West	-	96,121 (19%)	-	93,799 (19%)	-	111,834 (20%)

a: continuous variables presented as means and standard errors; categorical variables presented as weighted frequencies and proportions

b: proportions may not add up to 100% due to missing data or, in some cases, rounding error

Number of events with opioid abuse-related diagnoses

The number of events (unweighted) with opioid abuse-related diagnoses was 108,289; 110,785; and 127,905 in 2006, 2007, and 2008, respectively. The number of opioid abuse-related events (weighted) was 515,896; 506,837; and 564,559 for 2006, 2007, and 2008, respectively. Of these, the number and proportion of events for which the patient was admitted as an inpatient to the same hospital was 274,848 (53.28%); 281,385 (55.52%); and 303,468 (53.75%) for 2006, 2007, and 2008, respectively.

Proportion of opioid abuse-related ED visits by payer type

The number and proportion of opioid abuse-related ED visits by insurance status is shown in Table 4. We see a similar proportion distribution by insurance category for all three years. Medicaid was the expected primary payer for approximately 30% of these events in all three years, followed by self for 25% events, private insurance for 20% events, and Medicare for 17%.

Table 4: Number and proportion of emergency department visits by insurance category for 2006, 2007, and 2008 (weighted)

Insurance category	**Frequency (%)**		
	2006	**2007**	**2008**
Medicare	82,940 (16.08)	85,219 (16.81)	98,317 (17.41)
Medicaid	151,198 (29.31)	150,805 (29.75)	171,014 (30.29)
Private	98,382 (19.07)	107,720 (21.25)	121,372 (21.50)
Uninsured	143,455 (27.81)	130,556 (25.76)	134,059 (23.75)
No charge[a]	14,934 (2.90)	9,855 (1.95)	10,673 (1.89)
Other[b]	23,584 (4.57)	21,082 (4.16)	26,513 (4.70)
Missing	1,403 (0.27)	1,600 (0.32)	2,611 (0.46)
Total	**515,896 (100.0)**	**506,837 (100.0)**	**564,559 (100.0)**

a: includes charity funding, treatment as part of special research, medically indigent patient, or free care

b: includes Worker's Compensation, CHAMPUS, CHAMPVA, Title V, and other government programs

Figure 5 shows the trend in the total number of opioid abuse-related ED events from 2006-08. The data show an overall increase in total opioid abuse-related ED visits in the US population from 515,896 in 2006 to 564,559 in 2008, a 9.4% increase.

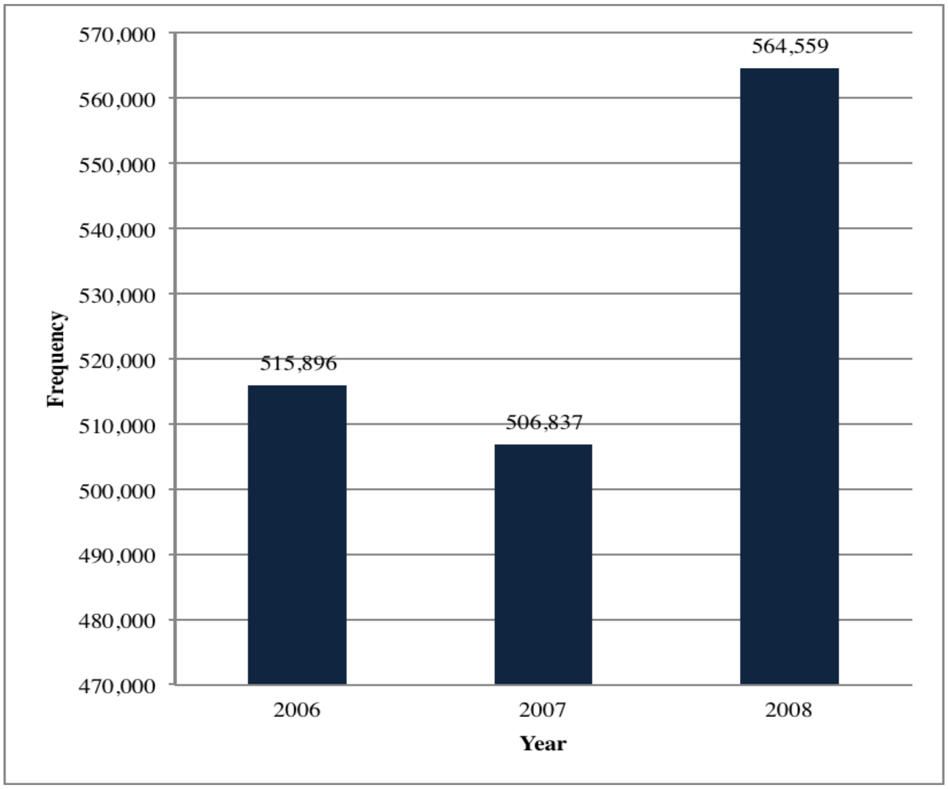


Figure 5: Total opioid abuse-related ED visits: 2006-08

Proportion of opioid abuse-related inpatient admissions by payer type

The number and proportion of opioid abuse-related ED visits that resulted in an inpatient admission at the same hospital, categorized by insurance status, is shown in Table 5. Medicaid was the expected primary payer for approximately 34% of these events in all three years, followed by Medicare for 21%, and private insurance for 20% events. Self-payment for opioid abuse-related events showed some variation in proportion from 21.85% in 2006 to 16.54% in 2008.

Table 5: Number and proportion of inpatient admissions by insurance category for 2006, 2007, and 2008 (weighted)

Insurance category	**Frequency (%)**		
	2006	**2007**	**2008**
Medicare	56,131 (20.42)	59,655 (21.20)	66,023 (21.76)
Medicaid	87,511 (31.84)	94,529 (33.59)	105,791 (34.86)
Private	49,783 (18.11)	55,457 (19.71)	60,522 (19.94)
Uninsured	60,067 (21.85)	51,898 (18.44)	50,204 (16.54)
No charge[a]	6,427 (2.34)	6,103 (2.17)	5,684 (1.87)
Other[b]	14,584 (5.31)	13,160 (4.68)	14,791 (4.87)
Missing	345 (0.13)	583 (0.21)	453 (0.15)
Total	**274,848 (100.0)**	**281,385 (100.0)**	**303,468 (100.0)**

a: includes charity funding, treatment as part of special research, medically indigent patient, or free care

b: includes Worker's Compensation, CHAMPUS, CHAMPVA, Title V, and other government programs

Figure 6 shows the total number of opioid abuse-related ED events resulting in inpatient admissions from 2006-08. There was an increase in the absolute number of opioid abuse-related ED events resulting in inpatient admissions to the same hospital. However, there was little variation in the proportion of ED visits with subsequent inpatient admission – 53.28%, 55.52%, and 53.75% in 2006, 2007, and 2008, respectively.

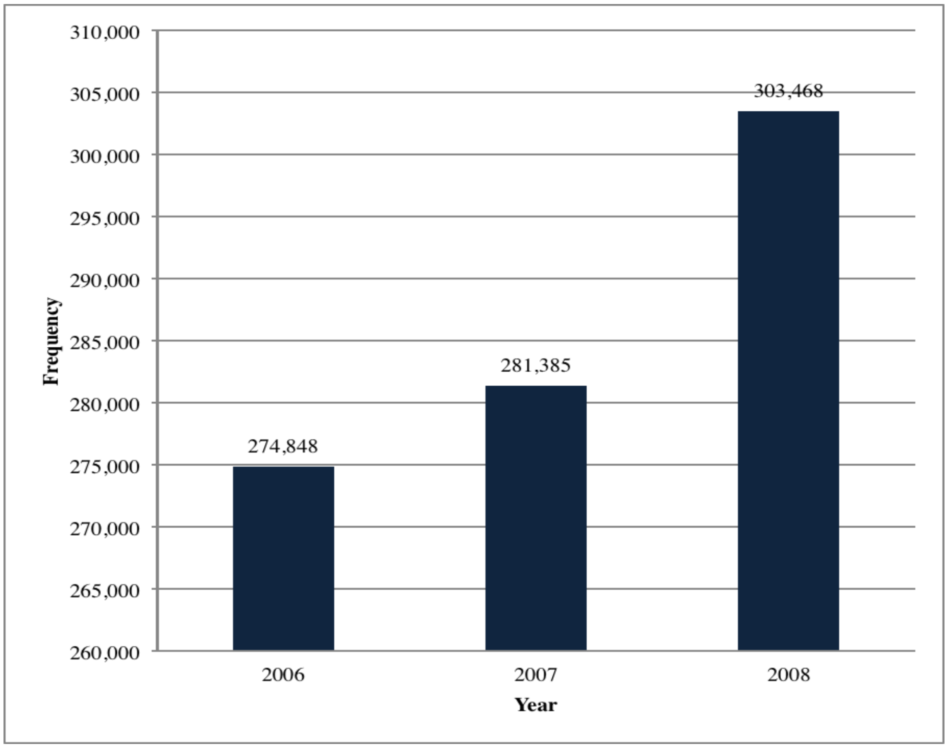


Figure 6: Total opioid abuse-related ED events resulting in inpatient admissions: 2006-08

Total charges billed

All charges are reported as national estimates in 2010 US dollars. The total charges billed for opioid abuse-related events in 2006, 2007, and 2008 are shown in Table 6. Total charges decreased 2.75% between 2006 and 2008.

Table 6: Total weighted charges by year (in 2010 billions USD)

Year	**Total charges**	**Confidence limits (95%)**	
		Lower	**Upper**
2006	9.79	8.31	11.3
2007	9.59	8.34	10.8
2008	9.52	8.39	10.7

The total charges, categorized by insurance status, for 2006, 2007, and 2008, are presented in Table 7. Events for which the expected primary payer was Medicaid had the highest total charges – $3.18 billion, $3.25 billion, and $3.26 billion for 2006, 2007, and 2008, respectively, followed by Medicare for all three years.

In all three years, charges for events in which the patient was admitted as an inpatient to the same hospital were substantially larger than for events in which the patient was treated and released from the ED (Table 8).

Table 7: Total weighted charges by year and insurance category (in 2010 billions USD)

Insurance category	2006			2007			2008		
	Total Charges	Confidence limits (95%)		Total Charges	Confidence limits (95%)		Total Charges	Confidence limits (95%)	
		Lower	Upper		Lower	Upper		Lower	Upper
Medicare	2.05	1.85	2.25	2.24	2.01	2.47	2.37	2.11	2.63
Medicaid	3.18	2.60	3.76	3.25	2.69	3.80	3.26	2.55	3.98
Private	1.73	1.52	1.95	1.72	1.50	1.94	1.76	1.58	1.94
Self-pay	2.00	1.36	2.64	1.60	1.17	2.04	1.42	1.22	1.62
No charge[a]	0.17	0.12	0.22	0.18	0.09	0.28	0.17	0.08	0.26
Other[b]	0.64	0.45	0.84	0.58	0.36	0.79	0.52	0.42	0.63

a: includes charity funding, treatment as part of special research, medically indigent patient, or free care

b: includes Worker's Compensation, CHAMPUS, CHAMPVA, Title V, and other government programs

Table 8: Total weighted charges for opioid abuse-related routine emergency department visits and those resulting in inpatient admissions (in 2010 billions USD)

Discharge disposition	2006			2007			2008		
	Total Charges	Confidence limits (95%)		Total Charges	Confidence limits (95%)		Total Charges	Confidence limits (95%)	
		Lower	Upper		Lower	Upper		Lower	Upper
Routine (treat-and-release)	0.36	0.29	0.43	0.37	0.31	0.43	0.45	0.40	0.49
Inpatient admission	9.32	7.89	10.70	9.11	7.90	10.30	8.96	7.85	10.10

Mean charges

The national estimates of average unadjusted per-event charges for 2006, 2007, and 2008 are presented in Table 9. Mean unadjusted charges were similar for 2006 and 2007; there was an approximately 10% decrease from 2007 to 2008.

Table 9: Overall mean (weighted, unadjusted) charges per event by year (in 2010 USD)

Year	Mean[a]	Confidence limits (95%)	
		Lower	Upper
2006	20,651	18,454	22,849
2007	20,373	18,363	22,383
2008	18,384	16,660	20,108

a: all charges rounded to the nearest dollar

National estimates of average unadjusted per-event charges categorized by insurance status are shown in Table 10. Events where Medicare was the expected primary payer had the highest mean charges in all three years, followed by events covered by Medicaid, private insurance, and self-payment. Compared to events where the primary payer was expected to be private insurance, events in which the expected primary payer was Medicare had significantly higher mean charges in 2006, 2007, and 2008 ($t = 8.83$, $p < 0.001$; $t = 11.17$, $p < 0.001$; and $t = 13.27$, $p < 0.001$, respectively). We found that mean charges for events covered by Medicaid were higher than those for events covered by private insurance in all three years, reaching statistical significance in 2007 and 2008 ($t = 4.46$, $p < 0.001$; and $t = 3.05$, $p = 0.002$, respectively). Opioid abuse-related events in uninsured patients resulted in significantly lower mean charges compared to privately insured patients in 2006, 2007, and 2008 ($t = -4$, $p < 0.001$; $t = -4.28$, $p < 0.001$; and $t = -7.28$, $p < 0.001$, respectively). Events that resulted in inpatient admissions to the same hospital as the ED visit, had significantly higher mean unadjusted charges in 2006, 2007, and 2008 ($t = 16.47$, $p < 0.001$; $t = 18.22$, $p < 0.001$; and $t = 19.25$, $p < 0.001$, respectively) (Table 11).

Table 10: Mean (weighted, unadjusted) charges per event by year and insurance category (in 2010 USD)

Insurance category	2006			2007			2008		
	Mean[a]	Confidence interval (95%)		Mean[a]	Confidence interval (95%)		Mean[a]	Confidence interval (95%)	
		Lower	Upper		Lower	Upper		Lower	Upper
Medicare	26,569	24,609	28,529	27,954	25,881	30,027	26,206	24,210	28,202
Medicaid	22,440	18,965	25,915	22,751	19,686	25,817	20,447	17,285	23,608
Private	19,375	17,477	21,273	17,201	15,166	19,235	16,038	14,683	17,393
Self-pay	15,330	12,831	17,829	13,467	11,414	15,520	11,650	10,384	12,917
No charge[b]	11,438	8,262	14,613	18,526	14,148	22,903	16,029	10,934	21,123
Other[c]	33,791	25,813	41,769	33,402	22,988	43,817	22,552	18,580	26,525

a: rounded to the nearest dollar

b: includes charity funding, treatment as part of special research, medically indigent patient, or free care

c: includes Worker's Compensation, CHAMPUS, CHAMPVA, Title V, and other government programs

Table 11: Mean (weighted, unadjusted) charges per event for opioid abuse-related routine ED visits and those resulting in inpatient admissions (in 2010 USD)

Discharge disposition	2006			2007			2008		
	Mean[a]	Confidence interval (95%)		Mean[a]	Confidence interval (95%)		Mean[a]	Confidence interval (95%)	
		Lower	Upper		Lower	Upper		Lower	Upper
Routine (treat-and-release)	2,390	2,206	2,575	2,394	2,198	2,591	2,470	2,303	2,637
Inpatient admission	34,018	30,158	37,878	32,517	29,171	35,862	29,721	26,854	32,586

a: rounded to the nearest dollar

The overall adjusted national estimates for per-event charges for 2006, 2007, and 2008 are presented in Tables 12. These estimates were adjusted for demographic and clinical characteristics such as age, sex, income quartile for zip code, patient's residence, location, US Census region in which hospital is located, number of comorbidities, primary payer for event, discharge disposition from the ED, and various comorbidities.

Table 12: Overall mean (weighted, adjusted) charges per event by year (in 2010 USD)

Year	Mean[a]	Confidence limits (95%)	
		Lower	Upper
2006	19,413	18,353	20,474
2007	19,560	18,584	20,536
2008	17,690	16,763	18,617

a: rounded to the nearest dollar.

National estimates of average unadjusted per-event charges categorized by insurance status are shown in Table 13. Events that had Medicare as the primary expected payer had the highest adjusted mean charges in all three years, followed by events where the expected payer was Medicaid, private insurance, and self. Compared to events covered by private insurance, Medicare-covered events had significantly higher adjusted mean charges in 2006, 2007, and 2008 ($t = 17.61$, $p < 0.001$; $t = 18.63$, $p < 0.001$; and $t = 21.46$, $p < 0.001$, respectively). Events covered by Medicaid also had significantly higher adjusted mean charges in all three years compared to events covered by private insurance ($t = 4.37$, $p < 0.001$; $t = 6.07$, $p < 0.001$; and $t = 3.75$, $p < 0.001$, respectively). Opioid abuse-related events in uninsured patients resulted in significantly lower adjusted mean charges compared to privately insured patients in 2006, 2007, and 2008 ($t = -6.8$, $p < 0.001$; $t = -6.8$, $p < 0.001$; and $t = -11.16$, $p < 0.001$, respectively). Events resulting in inpatient admissions to the same hospital as the ED visits had significantly higher adjusted mean charges in 2006, 2007, and 2008 ($t = 51.82$, $p < 0.001$; $t = 42.13$, $p < 0.001$; and $t = 36.45$, $p < 0.001$, respectively) (Table 14).

Table 13: Overall mean (weighted, adjusted) charges per event by year and insurance category (in 2010 USD)

Insurance category	2006			2007			2008		
	Mean[a]	Confidence interval (95%)		Mean[a]	Confidence interval (95%)		Mean[a]	Confidence interval (95%)	
		Lower	Upper		Lower	Upper		Lower	Upper
Medicare	28,241	26,996	29,485	30,431	29,047	31,815	28,313	26,862	29,764
Medicaid	20,891	19,237	22,544	20,668	19,257	22,080	18,511	16,870	20,152
Private	17,636	16,747	18,525	16,503	15,485	17,521	15,562	14,735	16,389
Self-pay	13,545	12,251	14,839	12,588	11,646	13,530	10,638	10,055	11,223
No charge[b]	11,051	9,549	12,554	18,739	14,946	22,532	15,554	12,751	18,356
Other[c]	27,211	24,230	30,193	27,611	24,304	30,918	20,047	17,682	22,412

a: rounded to the nearest dollar.

b: includes charity funding, treatment as part of special research, medically indigent patient, or free care.

c: includes Worker's Compensation, CHAMPUS, CHAMPVA, Title V, and other government programs.

Table 14: Mean (weighted, adjusted) charges per event for opioid abuse-related routine ED visits and those resulting in inpatient admissions (in 2010 USD)

Discharge disposition	2006			2007			2008		
	Mean[a]	Confidence interval (95%)		Mean[a]	Confidence interval (95%)		Mean[a]	Confidence interval (95%)	
		Lower	Upper		Lower	Upper		Lower	Upper
Routine (treat-and-release)	2,564	2,470	2,658	2,577	2,513	2,642	2,583	2,538	2,628
Inpatient admission	34,104	32,868	35,340	33,528	32,068	34,987	31,402	29,837	32,968

a: rounded to the nearest dollar

Association of demographic and clinical covariates with opioid abuse-related hospital charges

Potential predictors of opioid abuse-related hospital charges for 2006, 2007, and 2008 are presented in Tables 15, 16, and 17, respectively. All coefficients are presented as arithmetic mean ratios. For example, for a continuous variable like age, a coefficient of 1.003 (as it is in 2006) would be interpreted as – the ratio of the arithmetic mean of total charges for 2 patients, one older than the other by 1 year, would be 1.003 or that for every 1 year increase in age, mean total charges would increase by 0.3%. For a categorical variable, this ratio would be between total charges for a specific category versus the reference category. For example, in 2006, the coefficient for inpatient admission to the same hospital from the ED was 6.7898. This can be interpreted as – the mean charges for an event where the patient was transferred to the wards from the ED was approximately 7 times the mean charges for an event where the patient was treated and released from the ED ("treat-and-release" or "routine" being the reference category in this case).

Using three different regression analyses for the three years to determine predictors of hospital charges of opioid abuse-related events ensures robustness of associations. Table 18 shows whether the overall null hypotheses (over three years) were rejected or not. The variables that were significantly ($p < 0.01$) positively associated with total charges in all three years include: age; number of diagnoses; transfer from ED to short-term hospital versus treat-and-release visit; transfer from ED to other facilities like skilled nursing facility or intermediate care versus treat-and-release visits; expected primary payer category – other (Worker's Compensation, CHAMPUS, CHAMPVA, Title V, and other government programs) versus private insurance; presence of pericarditis, endocarditis, myocarditis, or cardiomyopathies; presence of respiratory infections; respiratory failure; gastrointestinal hemorrhage; and acute pancreatitis. The variables that were significantly ($p < 0.01$) negatively associated with total charges include: presence of anxiety disorders, bipolar disorder, depression, and alcohol-related disorders; and history of prior substance abuse. The variables that were not significantly ($p > 0.01$) associated with total charges in all three years include: gender; patient's county of residence – large fringe, medium, and small metropolitan (versus large central metropolitan); income quartile for ZIP code; presence of hepatitis; presence of schizophrenia; presence of chronic pancreatitis; and poisoning by psychotropic drugs. All other independent variables included in the model had statistically inconsistent results over the three years (e.g., $p < 0.01$ in one year and > 0.01 in the other two); the null hypothesis for such variables cannot be rejected.

Table 15: Log-linked gamma regression to assess potential predictors for ED and inpatient hospital charges for opioid abuse-related events (2006)

Variable	Coefficient[a]	p-value[b]
Age	**1.0030**	**<0.001**
Sex (ref = male)	1.0152	0.173
Number of comorbidities	**1.1089**	**<0.001**
Residence: (ref = Large central metropolitan)		
Large fringe metropolitan	0.9885	0.892
Medium metropolitan	0.9095	0.299
Small metropolitan	0.8640	0.097
Micropolitan	**0.7141**	**<0.001**
Not micro- or metropolitan	**0.7162**	**<0.001**
Median income: (ref = $1-$37,999)		
$38,000-$46,999	0.9987	0.975
$47,000-$61,999	0.9324	0.102
$62,000 or more	0.9120	0.052
Disposition: (ref = routine/treat-and-release)		
Transfer - short-term hospital	**1.8544**	**<0.001**
Transfer - other	**1.4830**	**<0.001**
Home health	**2.2682**	**<0.001**
Discharge against medical advice	**1.1138**	**0.007**
Inpatient admission to same hospital	**6.7898**	**<0.001**
Died in ED	**1.8298**	**<0.001**
Destination unknown, not admitted	**0.5357**	**<0.001**
Destination unknown, discharged alive	No event	No event
Expected primary payer: (ref = private insurance)		
Medicare	**0.8909**	**<0.001**
Medicaid	**0.8795**	**<0.001**
Self-pay	1.0417	0.109
No charge	**0.7917**	**0.006**
Other	**1.1471**	**0.006**
Region: (ref = Northeast)		
Midwest	**0.7160**	**<0.001**
South	**0.7451**	**0.002**
West	1.2205	0.067
HIV	1.0314	0.576
Hepatitis	0.9907	0.767
Herpes simplex	**0.7774**	**<0.001**
Neoplasms	1.0317	0.354
Anxiety disorder	**0.8379**	**<0.001**
Bipolar disorder	**0.8379**	**<0.001**
Depression	**0.8617**	**<0.001**
Schizophrenia	1.0546	0.111
Alcohol-related disorders	**0.9132**	**<0.001**
Suicide and intentional self-inflicted injury	**0.7340**	**<0.001**
History of mental illness	**0.8670**	**0.001**
History of substance-related disorders	**0.8544**	**<0.001**
Coma, stupor, and brain damage	1.0135	0.551
Cardiac tissue disorders (peri-, endo-, myocarditis; cardiomyopathies)	**1.5009**	**<0.001**
Cerebrovascular disease	**1.3747**	**<0.001**
Respiratory infection	**1.1978**	**<0.001**
Respiratory failure, insufficiency	**1.9938**	**<0.001**
Liver disease	1.0521	0.088
Gastrointestinal hemorrhage	**1.2058**	**<0.001**
Acute pancreatitis	**1.2070**	**<0.001**
Chronic pancreatitis	0.9443	0.232
Skin and subcutaneous tissue infections	1.0547	0.183
Poisoning by psychotropic drugs	0.9858	0.603

Variables for which null was rejected presented in bold

a: all coefficients presented as arithmetic mean ratio against reference category

b: statistically significant ($p < 0.01$) coefficients presented in bold

Table 16: Log-linked gamma regression to assess potential predictors for ED and inpatient hospital charges for opioid abuse-related events (2007)

Variable	Coefficient[a]	p-value
Age	**1.0019**	**0.004**
Sex (ref = male)	1.0236	0.081
Number of comorbidities	**1.1085**	**<0.001**
Residence: (ref = Large central metropolitan)		
Large fringe metropolitan	1.0402	0.62
Medium metropolitan	0.9929	0.936
Small metropolitan	0.8551	0.084
Micropolitan	0.8217	0.014
Not micro- or metropolitan	0.8194	0.016
Median income: (ref = $1-$38,999)		
$39,000-$47,999	1.0296	0.408
$48,000-$62,999	1.0343	0.491
$63,000 or more	1.0150	0.818
Disposition: (ref = routine/treat-and-release)		
Transfer – short-term hospital	**1.7820**	**<0.001**
Transfer – other	**1.4947**	**<0.001**
Home health	1.4092	0.047
Discharge against medical advice	1.0968	0.036
Inpatient admission to same hospital	**6.2972**	**<0.001**
Died in ED	**1.7015**	**<0.001**
Destination unknown, not admitted	**0.4977**	**<0.001**
Destination unknown, discharged alive	**0.4911**	**<0.001**
Expected primary payer: (ref = private insurance)		
Medicare	0.9772	0.485
Medicaid	0.9829	0.685
Self-pay	1.0844	0.012
No charge	1.0665	0.342
Other	**1.2178**	**0.01**
Region: (ref = Northeast)		
Midwest	0.8220	0.032
South	0.8643	0.163
West	**1.4037**	**0.007**
HIV	**0.8716**	**0.001**
Hepatitis	1.1321	0.058
Herpes simplex	No event	No event
Neoplasms	**1.0929**	**0.006**
Anxiety disorder	**0.8703**	**<0.001**
Bipolar disorder	**0.8822**	**<0.001**
Depression	**0.8782**	**<0.001**
Schizophrenia	1.0697	0.022
Alcohol-related disorders	**0.9311**	**0.003**
Suicide and intentional self-inflicted injury	0.8546	0.015
History of mental illness	**0.8535**	**<0.001**
History of substance-related disorders	**0.8807**	**<0.001**
Coma, stupor, and brain damage	1.0205	0.471
Cardiac tissue disorders (peri-, endo-, myocarditis; cardiomyopathies)	**1.3973**	**<0.001**
Cerebrovascular disease	**1.2613**	**<0.001**
Respiratory infection	**1.2243**	**<0.001**
Respiratory failure, insufficiency	**1.9242**	**<0.001**
Liver disease	**1.0846**	**0.002**
Gastrointestinal hemorrhage	**1.1754**	**0.001**
Acute pancreatitis	**1.2186**	**<0.001**
Chronic pancreatitis	0.9831	0.722
Skin and subcutaneous tissue infections	**1.1348**	**0.001**
Poisoning by psychotropic drugs	0.9524	0.031

Variables for which null was rejected presented in bold
a: all coefficients presented as arithmetic mean ratio against reference category
b: statistically significant ($p < 0.01$) coefficients presented in bold

Table 17: Log-linked gamma regression to assess potential predictors for ED and inpatient hospital charges for opioid abuse-related events (2008)

Variable	Coefficient[a]	p-value
Age	**1.0020**	**<0.001**
Sex (ref = male)	1.0108	0.373
Number of comorbidities	**1.1029**	**<0.001**
Residence: (ref = Large central metropolitan)		
Large fringe metropolitan	1.0129	0.867
Medium metropolitan	1.0018	0.982
Small metropolitan	0.8333	0.06
Micropolitan	**0.7942**	**0.002**
Not micro- or metropolitan	**0.7842**	**0.002**
Median income: (ref = $1-$38,999)		
$39,000-$48,999	1.0066	0.834
$49,000-$63,999	0.9773	0.55
$64,000 or more	0.9674	0.515
Disposition: (ref = routine/treat-and-release)		
Transfer - short-term hospital	**1.5374**	**<0.001**
Transfer - other	**1.5523**	**<0.001**
Home health	1.6058	0.131
Discharge against medical advice	**1.1712**	**<0.001**
Inpatient admission to same hospital	**5.4630**	**<0.001**
Died in ED	**1.8253**	**<0.001**
Destination unknown, not admitted	**1.3346**	**0.001**
Destination unknown, discharged alive	1.6023	0.041
Expected primary payer: (ref = private insurance)		
Medicare	0.9548	0.018
Medicaid	0.9411	0.067
Self-pay	1.0064	0.787
No charge	1.0785	0.534
Other	**1.1578**	**0.005**
Region: (ref = Northeast)		
Midwest	0.8495	0.03
South	0.8735	0.159
West	1.2498	0.017
HIV	0.9181	0.458
Hepatitis	1.0381	0.339
Herpes simplex	0.9884	0.877
Neoplasms	**1.1200**	**<0.001**
Anxiety disorder	**0.8925**	**<0.001**
Bipolar disorder	**0.8787**	**<0.001**
Depression	**0.9090**	**<0.001**
Schizophrenia	1.0503	0.064
Alcohol-related disorders	**0.9315**	**<0.001**
Suicide and intentional self-inflicted injury	**0.7743**	**<0.001**
History of mental illness	0.9541	0.13
History of substance-related disorders	**0.9308**	**<0.001**
Coma, stupor, and brain damage	**1.0821**	**0.001**
Cardiac tissue disorders (peri-, endo-, myocarditis; cardiomyopathies)	**1.3501**	**<0.001**
Cerebrovascular disease	**1.1779**	**<0.001**
Respiratory infection	**1.2298**	**<0.001**
Respiratory failure, insufficiency	**1.7849**	**<0.001**
Liver disease	**1.0744**	**0.003**
Gastrointestinal hemorrhage	**1.1224**	**0.001**
Acute pancreatitis	**1.3155**	**<0.001**
Chronic pancreatitis	1.0001	0.998
Skin and subcutaneous tissue infections	**1.1540**	**<0.001**
Poisoning by psychotropic drugs	0.9731	0.177

Variables for which null was rejected presented in bold

a: all coefficients presented as arithmetic mean ratio against reference category

b: statistically significant ($p < 0.01$) coefficients presented in bold

Table 18: Results of null hypotheses testing

Variable*, +, ++, +++	2006	2007	2008	Overall
Age	**Rejected**	**Rejected**	**Rejected**	**Rejected**
Sex (ref = male)	Not rejected	Not rejected	Not rejected	Not rejected
Number of comorbidities	**Rejected**	**Rejected**	**Rejected**	**Rejected**
Residence: (ref = Large central metropolitan)				
Large fringe metropolitan	Not rejected	Not rejected	Not rejected	Not rejected
Medium metropolitan	Not rejected	Not rejected	Not rejected	Not rejected
Small metropolitan	Not rejected	Not rejected	Not rejected	Not rejected
Micropolitan	Rejected	Not rejected	Rejected	Not rejected
Not micro- or metropolitan	Rejected	Not rejected	Rejected	Not rejected
Median income: (ref = $1-$38,999)				
$39,000-$47,999	Not rejected	Not rejected	Not rejected	Not rejected
$48,000-$62,999	Not rejected	Not rejected	Not rejected	Not rejected
$63,000 or more	Not rejected	Not rejected	Not rejected	Not rejected
Disposition: (ref = routine/treat-and-release)				
Transfer – short-term hospital	**Rejected**	**Rejected**	**Rejected**	**Rejected**
Transfer – other	**Rejected**	**Rejected**	**Rejected**	**Rejected**
Home health	Rejected	Not rejected	Not rejected	Not rejected
Discharge against medical advice	Rejected	Not rejected	Rejected	Not rejected
Inpatient admission to same hospital	**Rejected**	**Rejected**	**Rejected**	**Rejected**
Died in ED	**Rejected**	**Rejected**	**Rejected**	**Rejected**
Destination unknown, not admitted	**Rejected**	**Rejected**	**Rejected**	**Rejected**
Destination unknown, discharged alive	No event	Rejected	Not rejected	Not rejected
Expected primary payer: (ref = private insurance)				
Medicare	Rejected	Not rejected	Not rejected	Not rejected
Medicaid	Rejected	Not rejected	Not rejected	Not rejected
Self-pay	Not rejected	Not rejected	Not rejected	Not rejected
No charge	Rejected	Not rejected	Not rejected	Not rejected
Other	**Rejected**	**Rejected**	**Rejected**	**Rejected**
Region: (ref = Northeast)				
Midwest	Rejected	Not rejected	Not rejected	Not rejected
South	Rejected	Not rejected	Not rejected	Not rejected
West	Not rejected	Rejected	Not rejected	Not rejected
HIV	Not rejected	Rejected	Not rejected	Not rejected
Hepatitis	Not rejected	Not rejected	Not rejected	Not rejected
Herpes simplex	Rejected	No event	Not rejected	Not rejected
Neoplasms	Not rejected	Rejected	Rejected	Not rejected
Anxiety disorder	**Rejected**	**Rejected**	**Rejected**	**Rejected**
Bipolar disorder	**Rejected**	**Rejected**	**Rejected**	**Rejected**
Depression	**Rejected**	**Rejected**	**Rejected**	**Rejected**
Schizophrenia	Not rejected	Not rejected	Not rejected	Not rejected
Alcohol-related disorders	**Rejected**	**Rejected**	**Rejected**	**Rejected**
Suicide and intentional self-inflicted injury	Rejected	Not rejected	Rejected	Not rejected
History of mental illness	Rejected	Rejected	Not rejected	Not rejected
History of substance-related disorders	**Rejected**	**Rejected**	**Rejected**	**Rejected**
Coma, stupor, and brain damage	Not rejected	Not rejected	Rejected	Not rejected
Cardiac tissue disorders (peri-, endo-, myocarditis; cardiomyopathies)	**Rejected**	**Rejected**	**Rejected**	**Rejected**
Cerebrovascular disease	**Rejected**	**Rejected**	**Rejected**	**Rejected**
Respiratory infection	**Rejected**	**Rejected**	**Rejected**	**Rejected**
Respiratory failure, insufficiency	**Rejected**	**Rejected**	**Rejected**	**Rejected**
Liver disease	Not rejected	Rejected	Rejected	Not rejected
Gastrointestinal hemorrhage	**Rejected**	**Rejected**	**Rejected**	**Rejected**
Acute pancreatitis	**Rejected**	**Rejected**	**Rejected**	**Rejected**
Chronic pancreatitis	Not rejected	Not rejected	Not rejected	Not rejected
Skin and subcutaneous tissue infections	Not rejected	Rejected	Rejected	Not rejected
Poisoning by psychotropic drugs	Not rejected	Not rejected	Not rejected	Not rejected

Variables for which null hypotheses were consistently rejected in all three years are presented in bold
* - Significant positive association in all three years in green
+ - Significant negative association in all three years in red
++ - Non-significant association in all three years in black
+++ - Inconsistent association in blue

CHAPTER 4

DISCUSSION

This is the first study to examine and estimate healthcare costs of opioid abusers by insurance status, using a single, nationally representative database. The number of opioid abuse-related events was 515,986; 506,837; and 564,559 for 2006, 2007, and 2008, respectively. Data from DAWN estimate prescription opioid abuse-related ED visits as 247,669; 286,521; and 366,815 for 2006, 2007, and 2008, respectively.[45, 46, 47] Both DAWN and the NEDS are nationally representative samples. The reason for the difference in the estimates is likely to be due to differences in methods of data collection. DAWN data are collected by a retrospective review of ED medical records from an ED visit.[46] For a case to be considered a 'DAWN case', drug use must be recent and be related to the ED visit. For creation of an HCUP record, a medical coder classifies diagnosis and procedure codes at the time of discharge. Thus, an opioid abuser who comes to the ED with respiratory insufficiency, is stabilized, and admitted as an inpatient to the same hospital, where he is then given a secondary diagnosis of opioid abuse, may be missed during DAWN data collection but included in the creation of an HCUP record. Also, the numbers from DAWN data noted above represent specifically prescription opioid abuse. We used ICD-9-CM diagnosis codes to identify events associated with opioid abuse. As mentioned in the limitations section below, use of ICD-9-CM codes does not enable differentiation between prescription and nonprescription opioid abuse.

We are not aware of any study before this that has directly compared healthcare costs for opioid abuse by payer type. Birnbaum et al. used a ratio of per capita Medicaid healthcare spending to that of spending for privately insured persons from the Centers for Medicare and Medicaid Services.[27] This ratio was used as a proxy for public insurance in general and the analysis did not take into account other sources of public insurance (such as Medicare, CHAMPUS, CHAMPVA) which may have resulted in an inaccurate estimate. In another study, Birnbaum et al. used Florida Medicaid data and a spending ratio to adjust societal cost estimates to be nationally applicable. [28] A similar ratio was used to compute costs for Medicare and uninsured patients. Again, use of spending ratios might result in inaccurate estimates. Other studies have been carried out in either a privately insured population [29] or a Medicaid population. [30] Thus, this study is unique and makes a valuable contribution to existing literature of healthcare costs of opioid abusers.

The results of this study indicate an increase in opioid abuse-related ED visits as well as the number of inpatient admissions over the three-year period. This trend is in agreement with previous studies, including those conducted using nationally representative data such as the DAWN database.[6] However, the proportion of events for which patients are admitted to the same hospital has remained fairly constant (~54%). Total and mean charges decreased from 2006-2008. We analyzed average length-of-stay and found it to be fairly constant over the three years. However, a descriptive analysis number of procedures as well as of specific procedures is beyond the scope of this study; an exploration of both these variables may help explain the decreasing charges over the three years. We also have a poor understanding of the overall health status of patients reporting to the ED in the three years. An improvement in the baseline health status of patients could lead to decreasing per-event and total charges over the three-year period.

There is also a disparity in mean and total charges between treat-and-release ED visits and events where the patient is admitted as an inpatient from the ED to the same hospital (Table 11). The regression analyses showed that, compared to a treat-and-release visit, a visit resulting in inpatient admission had seven times higher charges billed, on average (Tables 15, 16, and 17). It was the single highest arithmetic mean ratio for all three years.

Medicaid and Medicare had higher mean (unadjusted) per-event charges. The regression analyses showed an inconsistent association between these two groups (versus private insurance) and total charges. In fact, in all three years, the Medicaid and Medicare groups had arithmetic mean ratios less than 1 (versus private insurance) (Tables 15, 16, and 17). In spite of this, adjusted mean charges for events covered by Medicare and Medicaid were much higher than for events covered by private insurance (Table 12). This may be explained by the fact that the majority of opioid abuse-related ED events covered by Medicare and Medicaid resulted in inpatient admissions. (Table 19)

Table 19: Proportion of inpatient admissions for events covered by Medicare, Medicaid, privately insurance, and self-pay by year

Insurance category	2006	2007	2008
Medicare	67.68%	70.00%	67.15%
Medicaid	57.88%	62.68%	61.86%
Private insurance	50.60%	51.48%	49.86%
Self-pay	41.87%	39.75%	37.45%

The high proportion of inpatient admissions in these groups of patients is likely to drive the adjusted means up to exceed the mean charges of events covered by private insurance. Further analysis is needed to explore the question of why 60-70% of Medicare- or Medicaid-covered opioid abusers get admitted as inpatients subsequent to an ED visit. It could be because these patients may have poorer health status than their privately insured counterparts or due to reimbursement strategies. Answers to such questions are beyond the scope of this study.

Since no study has reported charges as an estimate of healthcare costs for opioid abuse, we compared these estimates to cost estimates from previous literature. In a study by White et al., per-capita direct costs for privately insured opioid abusers were estimated at $15,884 (in 2003 US dollars). [29] Unadjusted, per-event charges for privately insured opioid abusers in the current study were $19,375; $17,201; and $16,038 (in 2010 US dollars) for 2006, 2007, and 2008, respectively. The study by White et al. included outpatient costs and prescription drug claim costs in addition to the cost categories included in this study (ED and inpatient). Since the estimates reported by White are in 2003 US dollars, for a greater number of cost categories, per-patient (i.e., not per-event), a direct comparison of aggregated data may not be suitable. However, it is noteworthy that approximately 98% of the total cost of ED visits and inpatient stays in the White et al. study were found to be hospital inpatient stay costs. A similar calculation for our study showed approximately 93% of the charges to be attributable to hospital inpatient stays.

McAdam-Marx et al. also assessed predictors of healthcare costs for opioid abuse. [30] The researchers used two years of data from Medicaid Analytic eXtract (MAX) files. They found that the presence of acute pancreatitis, gastrointestinal bleeding, and endocarditis were significantly positively associated with medical costs of opioid abusers. We got similar results in the current study. However, McAdam-Marx et al. also found presence of psychiatric disorders, HIV/AIDS, skin infections, liver disease, hepatitis, and herpes simplex to be significantly positively associated with costs of opioid abusers; we found these comorbidities to either be negatively associated or not significantly associated with charges. The difference in results between the two studies could be due to the differences in study populations. The NEDS is a nationally representative dataset while the MAX dataset includes only Medicaid patients.

Limitations

Use of ICD-9-CM diagnosis codes for patient selection has some limitations. As noted earlier, there is a considerable lack of clarity in interpretation of the terms abuse, dependence, and addiction. As a result, given that miscoding of ICD-9-CM codes is a possibility, we grouped all opioid abuse-related ICD-9-CM diagnosis codes for case identification, so that the composite group of opioid "abusers" consists of cases diagnosed with abuse, dependence, or poisoning with opioids. We did, however, exclude those cases that were clinically diagnosed as abusing heroin (a nonprescription opioid). We did this to get the best possible estimates for prescription opioid abusers. Use of ICD-9-CM diagnosis codes does not enable complete differentiation between prescription and nonprescription opioid abuse. Future research could focus on methods to distinguish prescription from nonprescription opioid abuse. Use of ICD-9-CM codes helps identify only those cases that have been clinically diagnosed with opioid abuse, dependence, or misuse. Opioid abuse may be under-diagnosed due to a stigma associated with it; [48] thus, generalization of the results to the population of undiagnosed opioid abusers may not be valid. Also, persons using opioids nonmedically but not needing emergency medical attention were not included in the current analysis. Thus, this analysis is not a complete cost analysis of opioid abusers as only those abusers who are captured by the hospital ED system are included.

HCUP reports charge, and not cost, data. Cost-to-charge ratio files are available for the SID, the NIS, and the KID, but not for the NEDS. Even though using charge data probably overestimates cost to the hospital, it still captures the differences in resource use by payer status. Development of cost-to-charge ratio files for the NEDS in the future will help us better understand the healthcare burden of opioid abuse on hospitals. This analysis includes only charges billed by the hospital. It is not an estimation of societal cost, as it does not take into account lost productivity costs, caregiver costs, and other non-medical costs.

The data do not have any patient identifiers and are event-level rather than patient-level data. Consequently, multiple records may be present in the data for a patient who visited the ED multiple times in a given year. Also, a patient may be transferred from one ED to another or from an ED to another hospital. Records (and by extension, charges) for such transfers may or may not be included in the NEDS because the NEDS is a 20% stratified, random sample of all ED visits in a year. [38] These issues could lead to charges being misestimated.

The current study analyzed specific comorbidities as predictors for charges but not specific procedures. Number of procedures as well as specific procedures are likely to have an impact on charges billed. However, both of these variables were outside the scope of this study. Future research could assess the significance of procedures on total charges billed.

Charges for events that have opioid abuse-related diagnosis codes may not specifically be due to abuse. Since we used a broad definition of abuse (all principal and secondary abuse-related diagnoses), the charges may be associated with comorbidities and the patient may just have a history of opioid abuse. The charges estimated in this study are not due to opioid abuse, but those associated with opioid abusers. It would be useful to know the temporal pattern and associations between the comorbidities studied and the diagnosis of opioid abuse; it would result in a better understanding of costs attributable to opioid abuse versus those attributable to other causes in the same patients. However, a longitudinal data set may be better suited to that objective.

Strengths

This study has some notable strengths. It is the first study to estimate healthcare costs (or part thereof) of opioid abusers using a single, nationally representative database. Use of the NEDS helped compute national estimates using the weights as well as the survey design specifications provided. Furthermore, all insurance groups were represented in the dataset, enabling a direct comparison of estimated costs at the national level.

After determining a raw estimate, mean charges were adjusted for various demographic and clinical factors, thus providing a better estimate of average per-event charges. The "adjustment" was done using a regression model with appropriate distribution and link specification. The appropriateness of the distribution in the generalized linear model was validated using the modified Park's test and was strongly indicative of the distribution function proposed. Thus, the model used in this study was statistically and mathematically validated.

The use of separate regression models for each year of data was also one of the strengths of this study. Use of multiple models helped in validating the robustness of the coefficients. Coefficients were assessed as being consistently significantly associated, consistently non-significantly associated, or inconsistently associated with charges. This approach helped in identifying predictors that had a variable association with charges for opioid abuse-related events over the three-year period. Such variables may be significant in specific populations (like skin infections, liver disease, and herpes simplex in the

Medicaid population) [30] but overall, are not significantly related with hospital charges in opioid abusers.

This is also the fist study to use demographic variables such as patient's income quartile and urban-rural designation of county of residence. Such variables could impact access to care as well as the kind of care facilities available, which in turn can have an impact on charges borne.

Conclusions

We found an increase in the number of opioid abuse-related ED visits from 2006 to 2008. While the absolute number of inpatient transfers to the same hospital also increased from 2006 to 2008, the proportion remained fairly constant. We found a decrease in total and per-event charges of opioid abuse-related events over the three-year period, with mean charges for events resulting in inpatient admissions being about seven times more than mean charges for treat-and-release visits. A high proportion of inpatient admissions for Medicaid and Medicare patients resulted in higher unadjusted as well as adjusted mean charges for these two groups. Some significant, positive predictors of charges for opioid abuse patients include age; number of comorbidities; and presence of cardiac tissue disorders, respiratory infection, respiratory failure, gastrointestinal bleeding, and acute pancreatitis. Future research should focus on a method to separate prescription from nonprescription opioid abusers, the impact of specific procedures and services on costs, as well as the temporal pattern and associations of specific comorbidities and opioid abuse.

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