

Predictors, rates, and trends of opioid use disorder among patients hospitalized with chronic pancreatitis

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Abstract

Background Patients with chronic pancreatitis (CP) suffer from pain and receive increased opioid prescriptions with a high risk of opioid use disorder (OUD). We studied the predictors, trends and outcomes of OUD among patients hospitalized with CP.

Methods Records with CP (with/without OUD) were extracted from the Nationwide Inpatient Sample (NIS) 2012-2014, and the association of OUD with the burden of CP was calculated. We then charted the trends of OUD and its interaction with concomitant CP from NIS 2007-2014 (SAS 9.4).

Results In the period 2012-2014, 4349 (4.99%) of the 87,068 CP patients had concomitant OUD, with higher risk among patients who were young, females, white vs. Hispanics, and individuals with chronic back pain, arthritis, non-opioid substance use, mental health disorders, and those hospitalized in urban centers. OUD was associated with a longer hospital stay (6.9 vs. 6.5 days, $P=0.0015$) but no significant difference in charges (\$47,151 vs. \$49,017, $P=0.0598$) or mortality (1.64% vs. 0.74%, $P=0.0506$). From 2007-2014, the average yearly rate of OUD was 174 cases per 10,000 hospitalizations (174/10,000), almost 3 times higher among CP vs. non-CP (479/10,000 vs. 173/10,000, $P<0.001$), and it increased from 2007 to 2014 (135/10,000 to 216/10,000, $P<0.001$). The yearly increase was 2.7 times higher among patients with CP vs. non-CP (29.9/10,000 vs. 11.3/10,000 hospitalizations/year, $P<0.001$).

Conclusions CP is associated with higher rates and trends of OUD. Patients with CP at high risk of OUD may benefit from alternate analgesic regimens or surveillance for OUD when they are prescribed opioids.

Keywords Length of stay, pain, mental health, charges, mortality

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Introduction

Opioids are commonly prescribed for the management of chronic pain in the United States and there has been a surge in prescriptions over the last 2 decades [1-3]. However, as the prescription rates have increased, the potential for abuse and ensuing untoward effects of these medications has assumed significant public health significance [4]. According to the Centers for Disease Control and Prevention (CDC), 11.5 million Americans in 2016 self-reported misuse of prescription opioids, while 2.1 million had opioid use disorder (OUD), as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) as a problematic pattern of opioid use leading to clinically significant impairment or distress [5]. Furthermore, chronic opioid therapy is associated with higher mortality [6,7], amongst many other opioid-related adverse events that result in higher numbers of emergency room visits, prolonged hospital stays, increased costs, and healthcare

resource utilization [3,8-12], without necessarily providing lasting pain relief, or any improvement in quality of life or functional capacity [13]. The CDC has published prescription guidelines, while states have prescription monitoring programs in efforts designed to mitigate the scourge of inappropriate prescription and OUD [14,15].

Chronic pancreatitis (CP) is a complex inflammatory disease characterized by lasting, progressive scarring and irreversible damage to the pancreas, resulting in loss of function [16,17]. Consequently, it is an incurable condition with treatment focused on the alleviation of pain and management of complications relating to malabsorption and insulin dependence [16,18,19]. Patients with CP commonly present across various healthcare settings with recurrent abdominal pain due to pancreatic inflammation, hyperstimulation and neuropathy, contributing to a considerably decreased quality of life. As a result, healthcare providers are often faced with the challenging task of assessing and managing this debilitating pain [18,20]. Despite best efforts, including pharmacologic, endoscopic and surgical interventions, most patients remain symptomatic and suffer from complications [21]. Narcotics are frequently utilized as a central part of a stepwise approach to providing analgesia, but they are unfortunately strongly associated with a potential for side effects and increased risk of tolerance and dependency [18,20,21]. Nusrat *et al* identified opioid use among 51% of CP patients [22].

Despite the common utilization of opioids and the potential for misuse among patients with CP, the burden and risk factors for OUD among this patient group have not been evaluated in a large population study. Barth *et al* found that depression, quality of life, pain intensity, and alcohol use were associated with opioid misuse among patients with chronic non-alcoholic pancreatitis [23]. However, their study was limited to a subset of patients with CP in a single tertiary center. We therefore sought to estimate the national prevalence and trends of OUD among patients hospitalized with CP, using a nationwide analysis, and to identify clinical and demographic predictors of OUD in this patient population.

Patients and methods

Data source and study design

This study was a retrospective cross-sectional study of all hospital admissions with a discharge diagnosis of CP between 2012 and 2014. Data were extracted from the National Inpatient Database (NIS), maintained by the Agency for Healthcare Research and Quality (AHRQ) as a core component of the Healthcare Cost and Utilization Project (HCUP). The AHRQ also performs validation and quality control of the database [24]. As the largest publicly available all-payer inpatient healthcare database in the USA, the NIS provides national estimates of more than 7 million discharges per annum [24]. It also provides valuable data on patient demographics, 30 primary and secondary diagnoses, 15 inpatient procedures, hospital characteristics, insurance status, comorbidity measures,

hospitalization charges, and length of stay, while protecting identifying patient information [24]. The diagnoses and procedures were encoded with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The use of the NIS is exempt from an Institutional Review Board as there is no identifying patient information [25,26].

Study population

All adult (age ≥ 18 years) hospitalizations for CP from NIS 2012-2014 were used for the cross-sectional study, while all adult (age ≥ 18 years) hospitalizations from NIS 2007-2014 were used for the trend analysis (Fig. 1). Patients with comorbid CP were identified by the ICD-9-CM code 577.1, while those with comorbid OUD were identified by the ICD-9-CM codes 304.0, 304.7 and 305.5 [27-29].

Variables

Patients' characteristics were identified from the NIS: demographics, hospitalization, hospital level, and comorbid diseases. Demographic factors included were age, sex (male and female), race/ethnicity (Whites, Blacks, Hispanics, and

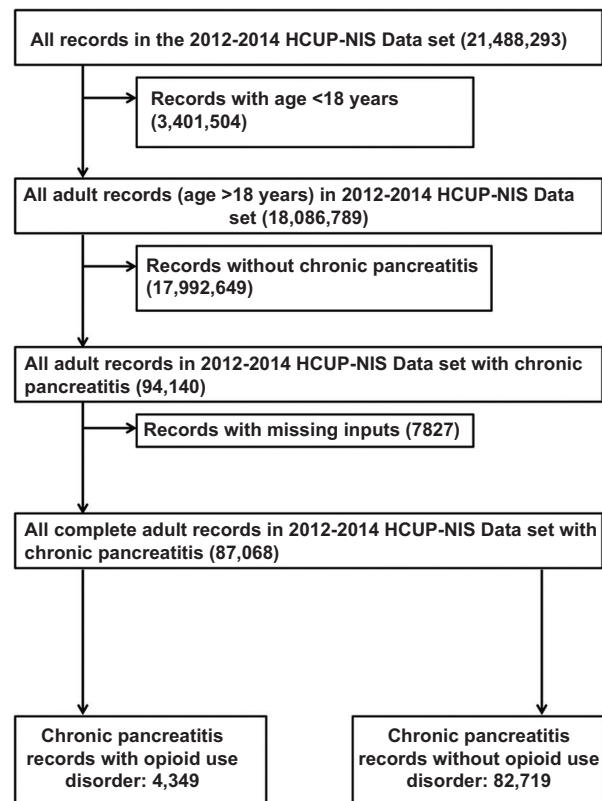


Figure 1 Selection flowchart for hospitalizations with chronic pancreatitis in the United States, NIS 2007-2014
NIS, National Inpatient Database (NIS); HCUP, Healthcare Cost and Utilization Project

other races), health insurance (Medicare, Medicaid, private, self-pay & others), income status (categorized into 4 according to the average household income of the zip-code where the patient lives), and geographic region (Northeast, Midwest, South and West). Hospitalization factors include whether the admission was during the weekend (no and yes), was a transfer from another facility (not a transfer, transfer from another acute care hospital, or transfer from a secondary/rehabilitation center), was an elective admission (no and yes), and in which season (autumn, winter, spring and summer). Hospital characteristics included the teaching status (rural non-teaching, urban non-teaching, and urban teaching), number of beds and hospital financial control. Based on the American Hospital Association annual survey of hospitals, the hospitals were categorized into 3 according to the number of acute care beds set up, hospital teaching status, and geographic region [30]. Roughly, small hospitals ranged from 1-249 beds, medium from 50-449 and large with 100+ beds, depending on the geographic region and teaching status. Similarly, hospital financial control was segregated into 3: public hospitals were categorized as government, voluntary hospitals as private non-profit, and proprietary hospitals as private profit [31]. Comorbid diseases were identified with ICD-9-CM codes (Supplementary Table 1) and included mental health disorders, chronic back pain, non-opioid substance abuse, chronic arthritis pain, and chronic headache. Possible etiologies of CP were identified and categorized into 3 groups: alcohol use, idiopathic, and others (biliary stones, family history of pancreatitis, autoimmune diseases, pancreatic cancer, hypercalcemia, hypertriglyceridemia, and cystic fibrosis). We also identified different comorbid diseases across all the organ systems and summarized them based on the Charlson-Deyo index [32]. Many of the comorbidities in this study have been used in many studies in the NIS [33-36].

The outcomes of the study were the prevalence of OUD, trends of OUD, and length of stay (LOS) during hospitalization.

Statistical analysis

The NIS data were extracted and analyzed using the Statistical Analysis System (SAS V.9.4, SAS Institute Inc, Cary, NC), and accounted for the complex multilevel survey methodology in the NIS [37,38] by eliminating the effect of the clustering of patients within the same hospital and hospitals within similar strata. Analyses incorporated recommendations from AHRQ [37], accounting for the complex survey methodology [38]. Numeric variables were summarized with mean and standard deviation and compared with Student's *t*-test, while categorical variables were summarized with percentages and compared using the Rao-Scott Chi-square test. Predictors of OUD among CP patients were identified with a multivariate survey logistic regression model with OUD as the outcome, and patients and hospital characteristics as the explanatory variables. Among CP patients, the association of OUD and mortality was calculated using multivariate generalized models, adjusting for demographic, comorbid,

and hospital level covariates. Similarly, multivariate models were used to calculate the association between OUD and LOS (negative binomial model) and charges (gamma models). Among all adult hospitalizations from 2007-2014, the yearly frequency of OUD was calculated and charted. The trend line was divided into 2 based on the presence of CP, then the interaction of CP with the trends of OUD was calculated using generalized linear models (Poisson distribution).

Results

Baseline characteristics

The baseline characteristics of the study population are presented in Table 1. In the years 2012-2014, we identified 87,068 patients with a primary discharge diagnosis of CP and stratified them by the presence or absence of concomitant OUD (Fig. 1). Of these patients, 4349 (4.99%) also had OUD. CP patients with or without OUD were predominantly male, White and were predominantly in the lowest quartile of income. CP patients with OUD were younger (mean age 46.9 ± 11.73 vs. 52.6 ± 14.72 years), and had a lower proportion of Medicare- and private-insured, but a higher proportion of Medicaid-insured patients compared to those without OUD. The West and Northeast regions had a higher proportion of patients with OUD. Compared with those without OUD, CP patients with opioid abuse were more likely to be admitted over the weekend and to be admitted non-electively. Urban, privately controlled non-profit hospitals had the highest proportions of patients with CP and OUD.

In addition, patients with CP and OUD were more likely to engage in non-opioid substance abuse (alcohol and non-opioid drugs) and included a higher proportion of patients with mental disorders. Although this group of patients had more pain-associated conditions, such as chronic back pain and headache, they had a smaller comorbidity burden in comparison to CP patients without OUD. There was no significant difference between the groups as regards hospital size or transfer admission status. Regarding the etiology and risk factors of CP, patients with alcohol use disorder were more likely to have OUD, while other risk factors for CP (idiopathic, and others) were higher among those without OUD (Table 1). All substance use disorders (alcohol, tobacco and other substance) were more predominant among subjects with OUD.

Predictors of opioid use disorder

Table 2 shows the demographic and clinical factors significantly associated with OUD in patients hospitalized with CP. On multivariate analysis, age, sex and race were independent predictors of OUD. Increasing age was associated with 21% (adjusted odds ratio [aOR] 0.79, 95% confidence interval [CI] 0.77-0.80) reduced odds of OUD while females had 6% greater odds compared to males. While Hispanic

Table 1 Characteristics of hospitalizations with chronic pancreatitis by opioid use disorder, NIS 2012-2014

Characteristics	No-opioid 82,719 (~413,595)	Opioid 4349 (~21,745)	P-value
Age, mean (SD), y	52.63 (14.72)	46.90 (11.73)	<0.001
Age, categorized, y			<0.001
18-45	18.84	27.41	
45-65	51.71	59.44	
>65	29.44	13.15	
Sex, %			0.3160
Male	55.04	54.20	
Female	44.96	45.80	
Race, %			0.0157
White	64.90	67.26	
Black	23.04	21.94	
Hispanic	7.79	7.40	
Other	4.27	3.40	
Insurance, %			<0.001
Medicare	39.43	33.85	
Medicaid	24.26	35.25	
Private	21.99	17.52	
Self-pay & others*	14.32	13.38	
Income, %			0.0799
Lowest quartile	36.34	34.90	
Second quartile	26.39	26.17	
Third quartile	20.93	21.06	
Highest quartile	16.34	17.87	
Region, %			<0.001
Northeast	18.34	23.66	
Midwest	22.79	20.44	
South	42.09	32.95	
West	16.78	22.95	
Admission at weekend, %			0.0031
No	76.47	74.52	
Yes	23.53	25.48	
Season, %			0.7002
Autumn	25.01	25.78	
Winter	24.90	24.47	
Spring	25.89	25.57	
Summer	24.21	24.19	
Transfer admission, %			0.2016
No	92.88	92.97	
From hospital	5.15	5.44	
From secondary health facility	1.97	1.60	

(Contd...)

Table 1 (Continued)

Characteristics	No-opioid 82,719 (~413,595)	Opioid 4349 (~21,745)	P-value
Elective admission, %			<0.001
No	90.95	93.21	
Yes	9.05	6.79	
Hospital teaching status, %			<0.001
Rural	10.04	6.58	
Urban non-teaching	31.41	32.79	
Urban teaching	58.54	60.63	
Hospital size, %			0.1973
Small	14.83	14.14	
Medium	27.63	26.58	
Large	57.54	59.28	
Hospital control, %			0.0037
Government	12.88	11.45	
Private, non-profit	73.35	76.50	
Private, profit	13.77	12.05	
Mental health disorders, %	28.11	46.29	<0.001
Chronic back pain, %	9.05	13.06	<0.001
Etiology of chronic pancreatitis, %			
Alcoholic	46.56	60.57	<0.001
Idiopathic	45.17	34.42	<0.001
Other causes/risk factors	12.87	9.70	<0.001
Biliary stones	4.92	2.71	<0.001
Family history of pancreatitis	0.11	0.07	0.4567
Autoimmune	1.52	1.40	0.5598
Pancreatic cancer	1.75	0.97	<0.001
Hypercalcemia	0.76	0.85	0.4952
Hypertriglyceridemia	3.79	2.94	0.0045
Cystic fibrosis	0.50	0.90	<0.001
Tobacco use, %	46.78	55.51	<0.001
Other substance use (not alcohol, tobacco nor opioid), %	9.52	36.68	<0.001
Charlson-Deyo comorbidity index, %			<0.001
Deyo: 0	32.30	37.96	
Deyo: 1-3	48.83	47.30	
Deyo: >3	18.87	14.74	

*Self-pay & others: Individuals without a health insurance or paying health fees out of pocket

SD, standard deviation, NIS, National Inpatient Database

ethnicity was associated with lower odds of OUD (aOR 0.84, 95%CI 0.77-0.93), Blacks and other ethnic groups were similar to Whites. Relative to individuals with private insurance, patients insured by Medicare or Medicaid had significantly higher odds of OUD, while those categorized as "Others" (self-pay and uninsured) showed no difference. Compared to the Northeast, the Midwest and South were both associated with

32-35% lower odds of opioid abuse amongst hospitalized CP patients, while the West had no difference. Urban teaching and non-teaching hospitals were significantly associated with OUD compared to rural. Individual comorbid conditions, such as mental health disorders, back pain, arthritis and headaches were significant predictors of OUD. Likewise, alcohol use and use of other substances (not alcohol, tobacco or opioid)

Table 2 Predictors of opioid use disorder among hospitalizations with chronic pancreatitis, NIS 2012-2014

Predictors	Adjusted odds ratio (95%CI)	P-value
Age, per 10-year increase	0.79 (0.77-0.80)	<0.001
Sex: female vs. male	1.06 (1.01-1.11)	0.0163
Race		0.0013
Black vs. White	0.95 (0.89-1.01)	
Hispanics vs. Whites	0.84 (0.77-0.93)	
Others vs. Whites	0.90 (0.79-1.01)	
Health insurance		<0.001
Medicare vs. private	1.29 (1.20-1.38)	
Medicaid vs. private	1.36 (1.27-1.45)	
Self-pay & others* vs. private	0.97 (0.89-1.05)	
Income status		0.0205
Lowest vs. highest quartile	1.01 (0.95-1.07)	
Second vs. highest quartile	1.01 (0.95-1.08)	
Third vs. highest quartile	1.11 (1.03-1.19)	
Weekend vs. weekday admission	1.03 (0.97-1.08)	0.3412
Season		0.0872
Autumn vs. winter	1.03 (0.97-1.10)	
Spring vs. winter	0.97 (0.91-1.04)	
Summer vs. winter	0.95 (0.89-1.02)	
Transfer status		0.1597
From acute care hospitals vs. none	1.01 (0.91-1.13)	
From secondary care facilities vs. none	0.82 (0.67-1.01)	
Non-elective vs. elective admission	1.08 (0.99-1.17)	0.1007
Hospital region		<0.001
Midwest vs. Northeast	0.65 (0.60-0.69)	
South vs. Northeast	0.68 (0.64-0.72)	
West vs. Northeast	1.05 (0.98-1.13)	
Hospital teaching status		<0.001
Urban non-teaching vs. rural	1.37 (1.25-1.51)	
Urban teaching vs. rural	1.46 (1.33-1.60)	
Hospital size		0.2244
Medium vs. small	1.07 (0.99-1.15)	
Large vs. small	1.06 (0.99-1.13)	
Hospital control		<0.001
Private non-profit vs. government	1.14 (1.06-1.23)	
Private for-profit vs. government	0.97 (0.88-1.07)	
Mental health disorders	1.66 (1.58-1.74)	<0.001
Back pain	1.46 (1.35-1.57)	<0.001
Arthritis	1.15 (1.08-1.23)	<0.001
Headaches	1.17 (1.05-1.31)	0.0057
Malignancy	0.88 (0.75-1.03)	0.1108
Etiology of chronic pancreatitis		
Alcoholic	1.31 (1.11-1.54)	0.0011
Idiopathic	0.96 (0.81-1.12)	0.5878
Other causes/risk factors	0.80 (0.71-0.90)	<0.001
Tobacco	1.01 (0.95-1.07)	0.8342
Other substances (not alcohol, tobacco, or opioid)	4.77 (4.52-5.03)	<0.001
Charlson-Deyo comorbidity index		0.2124
Deyo: 1-3 vs. 0	1.00 (0.95-1.06)	
Deyo: >3 vs. 1-3	0.94 (0.86-1.02)	

*Self-pay & others: Individuals without a health insurance or paying health fees out of pocket

CI, confidence interval, NIS, National Inpatient Database

were respectively associated with 31% (1.31, 95%CI 1.11-1.54; $P=0.0011$) and 380% (4.77, 95%CI 4.52-5.03; $P<0.001$) increased odds of having OUD. However idiopathic causes of CP were not associated with OUD, and other causes of CP were associated with 20% lower odds of OUD (0.80 95%CI 0.71-0.90; $P=0.0020$).

Outcomes of CP with OUD

Compared to patients without OUD (Table 3), those with OUD stayed longer (adjusted length of stay, 6.9 vs. 6.5 days, $P=0.0015$), after accounting for demographic, comorbid, and hospital variables. However, there was no difference in the hospital mortality rate (1.64 vs. 0.74%, $P=0.0506$) and charges between OUD and no-OUD (\$47,151 vs. \$49,017, $P=0.0598$).

Temporal trends of OUD

Temporal trends of OUD were analyzed between 2007 and 2014. The rate of OUD among all patients hospitalized in the United States rose steadily from 135 to 216 cases per 10,000 hospitalizations (1.35-2.16%), at an average rate of 11.41 cases per 10,000 hospitalizations per annum (Fig. 2A and Supplementary Table 2). When stratified by the primary diagnosis of CP (Fig. 2B), the OUD rate increased from 365 to 566 cases per 10,000 hospitalizations (3.6-5.6%) at a gradient of 30 cases per 10,000 hospitalizations per year (0.30%), culminating in an average frequency of 4.79%. With a frequency of 1.74%, OUD rates were lower in those without CP, consistently staying at below 220 cases per 10,000 hospitalizations (1.34-2.16%) and rising by only 11.3 cases per 10,000 hospitalizations per annum (0.11%) between 2007 and 2014. Thus, not only were individual annual rates of OUD about 2.8 times higher in patients with CP, the slope of the increase was almost 2.7 times steeper than in patients without CP (Fig. 2B).

Discussion

The management of chronic non-malignant pain conditions such as CP poses a significant challenge to clinicians, who

often rely on opioids to provide relief [39]. As a result, opioid prescription has spiked significantly in the last 2 decades in the United States, directly contributing to many undesirable consequences, amongst which is OUD [2,40]. This analysis of a large national database highlights the prevalence, trends and independent predictors of OUD among patients hospitalized with CP.

In our study population, 4.99% of patients with CP had coexisting OUD: approximately 1 in 20 patients. This frequency is higher than the reported national prevalence of 0.8% [41] and the prevalence observed in specific patient subgroups, such as those with inflammatory bowel disease (IBD) (2.2%) [42] and those undergoing cardiac surgery (0.2%) [43]. Several significant associated factors were identified, including younger age, female sex, insurance status, hospital region, and teaching status. Other independent predictors of OUD in the study cohort were mental health disorders, back pain, arthritis, and non-opioid substance abuse. These are consistent with the findings of previous studies in other diseases [44-46]. However, a recent single-center study of patients with pancreatitis reported that the frequency of persistent opioid use was 9% among patients with recurrent acute pancreatitis, while it was absent among patients with only pancreatitis [47]. The higher frequency (9%) in this study is probably because the patients had a closer longitudinal follow up on their prescriptions, unlike our study, which relied solely on ICD-9-CM codes. Another notable finding in this study is the steeper rise in the annual prevalence of OUD among patients with CP relative to the rest of the population. While the average annual prevalence of opioid abuse in all hospitalized patients steadily increased over the study period, the average prevalence rate in patients with CP was always greater and increased at approximately triple the annual rate observed in those without CP. Thus, CP is a significant driver of OUD trend among hospitalized patients.

The higher frequency of OUD observed among patients with CP firmly suggests CP as a risk factor for OUD. As a prominent and recurring cause of debilitating abdominal pain, often managed with opioids, CP potentially increases the risk of opioid abuse in afflicted individuals. The independent predictors of OUD identified in this study can assist healthcare providers to screen and identify at-risk individuals. This subgroup of patients should be offered alternative modalities of pain management, such as non-opioid analgesia, nerve blocks and endoscopic therapy, coupled with pancreatic enzyme

Table 3 Association of opioid use disorder and outcomes among hospitalizations with chronic pancreatitis, NIS 2012-2014

Outcome	Opioid use		Opioid use vs. no-use	
	Yes	No	Adjusted Odds/Mean ratio* (95%CI)	P-value
Length of stay, median (95%CI), days	6.9 (6.5-7.2)	6.5 (6.2-6.8)	1.05 (1.02-1.09)	0.0015
Total hospital charge, median (95%CI), \$US	47,151 (44,156-50,350)	49,017 (46,465-51,708)	0.96 (0.92-1.00)	0.0598
In-hospital mortality, %	1.64	0.74	0.70 (0.49-1.00)	0.0506

*Adjusted odds ratios were calculated for binary outcome (mortality), while adjusted mean ratio was calculated for numeric outcomes (length of stay, and hospital charges)

CI, confidence interval, NIS, National Inpatient Database

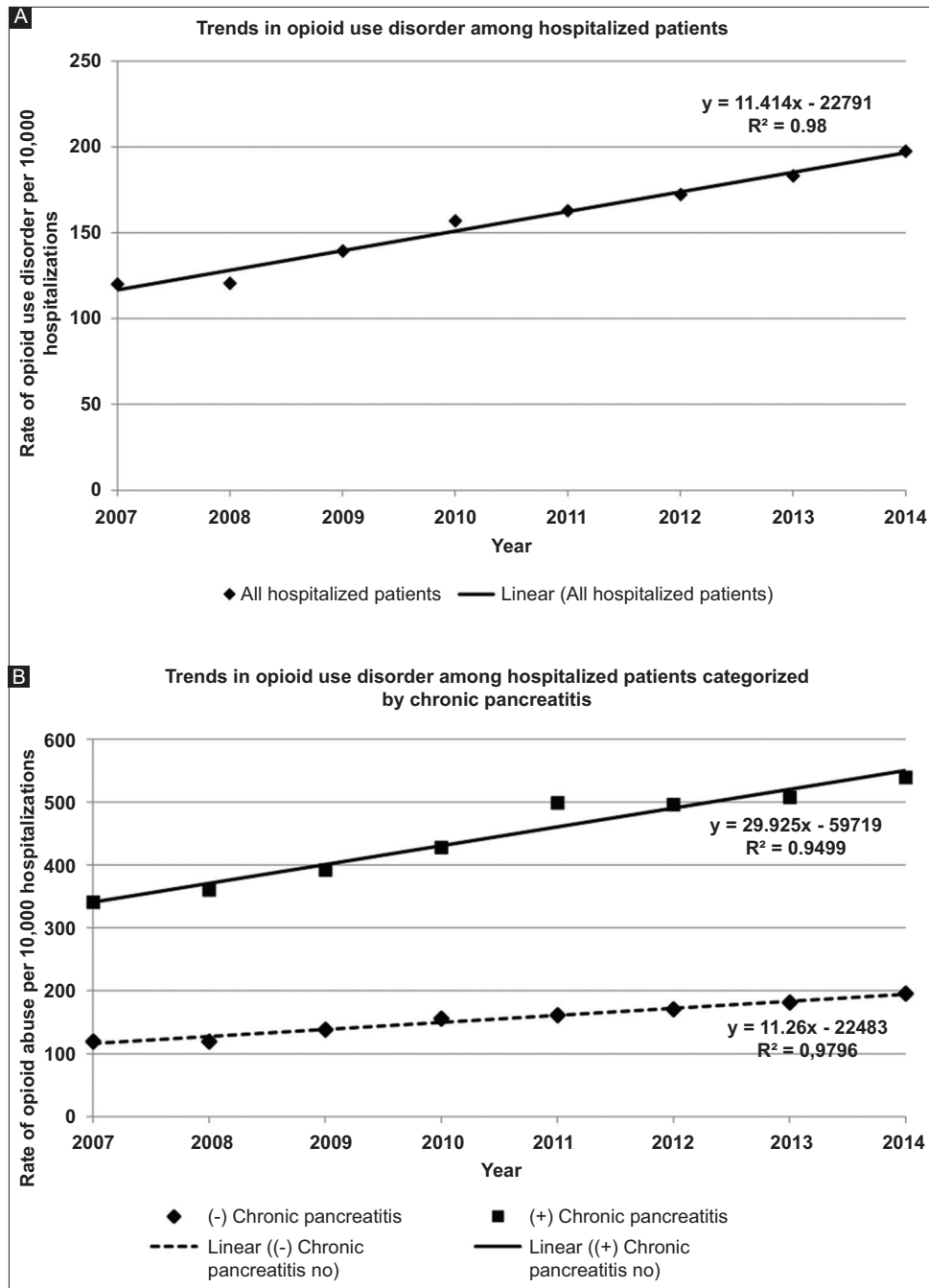


Figure 2 Annual prevalence of opioid use disorder among hospitalizations in the United States, 2007-2014. (A) Trends among all hospitalizations. (B) Trends among hospitalizations with vs. without chronic pancreatitis

supplementation and risk factor modification, including alcohol and tobacco abstinence [18,20,48,49]. An early surgical approach to treatment in qualified individuals has also been shown to be associated with improved outcomes [21,50-52]. Should opioids be required, patients should be educated and counseled on the potential side effects, and especially the risks of dependence and addiction [14]. As far as possible, opioids should serve as a bridge to a more sustainable treatment. They should be utilized at the minimum effective dose and duration [53]. Early referral of high-risk patients to

a pain specialist, anesthesiologist, endoscopist or surgeon, as indicated, may be prudent [51].

There was a significant association between mental disorders, Medicare and Medicaid insurance, and opioid abuse in patients hospitalized with CP. Depressive symptoms were reported to be associated with opioid misuse among patients with CP in the single-center study by Barth *et al* [23]. Psychiatric disorders have consistently been shown to predict OUD in multiple studies of patients with IBD, which is another potent gastrointestinal cause of chronic relapsing/remitting

abdominal pain [42,54,55]. This study also reveals a higher risk of OUD among patients insured with Medicaid and Medicare. With the expansion of Medicaid to cover healthcare for patients with substance abuse [56], CP patients with OUD are more likely to be Medicaid-insured. In a recent national study by Jeffery *et al*, opioid use rate was also found to be highest in Medicare vs. commercially-insured patients [57]. Likewise, chronic pain conditions, such as arthritis and back pain, were also identified as risk factors for opioid abuse, consistently with studies on other subsets of patients [58,59]. As in previous studies of acute pancreatitis [60] or other disease conditions, we found that females had higher odds of OUD. In addition to being more likely to be prescribed opioids at higher doses and longer duration for chronic pain [61,62], women are also biologically more susceptible to opioid dependence and addiction [63]. The higher odds of OUD among CP patients on government insurance (Medicare and Medicaid) compared to private insurance may be due to recent policy changes by private insurance companies to encourage better implementations of optimal prescription practice [64].

Patients with OUD had a longer LOS, which could be related to this patient group having a greater need for parenteral opiates and the longer time it may take to wean off these medications and transition to oral alternatives. Other plausible explanations include likely higher inpatient complications related to OUD, such as respiratory distress, constipation or altered mental status. Similarly, longer hospitalization stays have been described in IBD and orthopedic surgery patients with concomitant OUD [42,65]. While our analysis does not include data on the post-hospitalization outcomes of patients with CP with a diagnosis of opioid misuse, an understanding of the epidemiology of OUD in these patients is crucial to appreciating its potentially larger burden on the community. Since patients with CP show a higher OUD prevalence than both the population at large and other patient subgroups, and this prevalence is continuously rising, it is plausible that OUD in CP patients may be a major contributor to outpatient opioid-related complications and healthcare utilization. The similar in-hospital mortality rate and charges for CP patients with OUD and those without in our study only reflect events inside the hospital. Patient with OUD are known to have a higher prevalence of out-of-hospital opioid overdose, resulting in respiratory and cardiovascular arrest and, ultimately, in higher mortality [66,67].

This study was limited by the use of a de-identified database without access to individual patients or charts; thus, we are only able to determine the predictors of opioid abuse among hospitalized patients with CP and not the specific underlying reasons for this behavior. Additional studies are needed to elucidate the specific causes of OUD in this patient group. As the unit of entry in the NIS database is a hospitalization and not a specific individual, there may be multiple hospitalizations for the same person. Furthermore, other associated factors that may elevate the risk of OUD, such as pain severity or CP duration, were not available. Similarly, clinical details, such as imaging features of the pancreas (degree of calcification, enlargement, pancreatic duct diameter) and frequency of past endoscopic/surgical pancreatic procedures, were not available.

Limited to only inpatient data, we could not determine the potential influence of inpatient care on post-hospitalization outcomes. Despite these limitations, our population-based study has the strengths of including a large sample size and being nationally illustrative of the escalating burden of OUD in patients with CP, as well as its associated predictors.

To conclude, OUD affects a significant proportion of patients with CP and occurs at an increasing rate, almost 3 times the rate of those without CP. Young, female, Medicaid- and Medicare-insured patients are most susceptible. Other risk factors are mental health disorders, pain-associated conditions and non-opioid drug abuse. A recognition of predisposing preexisting demographic and clinical variables may help clinicians to better identify individuals who are most at risk of opioid dependence and abuse, guiding a more prudent utilization of opioids and alternative therapy in this patient group, thereby slowing and potentially reversing the increase in rates of OUD.

Summary Box

What is already known:

- Patients with chronic pancreatitis (CP) suffer debilitating pain, which results in an elevated risk of opioid prescription and opioid use disorder (OUD)
- Research on the prevalence, risk factors and outcomes of OUD is lacking among patients with CP

What the new findings are:

- The prevalence of OUD was 3 times higher among patients with CP vs. non-CP
- From 2007-2014, the prevalence of OUD increased among all hospitalizations, but at an almost 3 times higher rate among CP vs. non-CP patients
- Prevalent risk factors for OUD among CP patients include younger age, White vs. Hispanic race, hospitalizations in urban centers, and use of alcohol and other substances
- OUD was associated with a longer hospital stay, but no difference in mortality or hospital charges

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Supplementary Table

Supplementary Table 1 ICD-9-CM codes for identifying clinical conditions in the HCUP-NIS Dataset, 2007-2014

Clinical condition	ICD-9-CM codes, elixhauser comorbidity variables and clinical classification system codes
Chronic pancreatitis	577.1
Opioid use disorder	304.0, 304.7, 305.5
Mental health disorders	293, 294, 295, 296, 297, 298, 299, 300, 301, 302
Back pain	720, 721, 722, 723, 724
Arthritis	710-719, 725, 726, 727, 728, 729, 730-739
Headaches	346, 307.81, 784.0
Alcohol use	303.x, 305.3x, 291.x, 980.x, V11.3
Biliary stones	574.x
Family history of pancreatitis	V18.59
Autoimmune diseases	710.x
Pancreatic cancer	156.2, 157.x, V10.09
Hypercalcemia	275.42
Hypertriglyceridemia	272.1, 272.2
Cystic fibrosis	277.0
Tobacco use	305.1, 989.84, V15.82
Other substance use (neither alcohol, tobacco nor opioid)	292, 304.1-304.9, 305.2-305.4, 305.6-305.9, 648.3
Charlson-Deyo comorbidity index	Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. <i>Med Care</i> 2005;43:1130-1139.

NIS, National Inpatient Database (NIS); HCUP, Healthcare Cost and Utilization Project

Supplementary Table 2 Trends in opioid use disorder (cases per 10,000 hospitalizations) among adult hospitalizations, categorized by presence of chronic pancreatitis, NIS 2007-2014

Year	All patients	Chronic pancreatitis	
		No	Yes
2007	135.0	134.2	365.3
2008	137.1	136.1	386.7
2009	156.1	154.9	421.5
2010	175.7	174.3	453.2
2011	182.1	180.4	527.5
2012	192.0	190.3	521.4
2013	202.4	200.6	534.6
2014	216.4	214.5	566.2
2007-2014	174.0	172.5	478.8

NIS, National Inpatient Database