

Original Article

The Impact of Opioid Epidemic Trends on Hospitalised Inflammatory Bowel Disease Patients

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Abstract

Background and Aims: Opioid use disorder [OUD] has become a public health crisis among patients with chronic disease. Inflammatory bowel disease [IBD] patients are at high risk for OUD because they suffer from chronic relapsing-remitting pain. We aimed to describe the prevalence and trends in OUD-related diagnoses among hospitalised IBD patients.

Methods: A retrospective study was performed using weighted Nationwide Inpatient Sample data from 2005 to 2014. Adult IBD hospital visits and OUD-related diagnoses were identified using a previously published schema. Annual diagnoses were calculated. Characteristics associated with OUD were assessed using multivariable logistic regression. Associations between OUD and length of stay were assessed overall and separately for surgical and non-surgical stays.

Results: In all, 2.2% of 2585174 weighted discharges with any diagnosis of IBD also had an OUD-related diagnosis, with an 8.8% average annual increase. In multivariable analysis, Crohn's disease, public payer or no insurance, and psychiatric comorbidities were associated with a higher likelihood of OUD, whereas a primary diagnosis of an IBD-related complication was associated with a lower likelihood. An OUD-related diagnosis was associated with 0.84 days [95% confidence interval [CI] 0.71, 0.97] increased length of stay overall, 2.79 days [95% CI 1.44, 4.14] for surgical stays, and 0.71 days [95% CI 0.59, 0.82] for non-surgical stays.

Conclusions: OUD-related diagnoses are increasing among IBD patients and are associated with increased length of stay. With a rising prevalence, it is important to screen and diagnose OUD in IBD and refer patients for evidence-based treatment to address unmet patient needs and reduce health care utilisation.

Key Words: Substance abuse; Crohn's disease; ulcerative colitis

1. Introduction

Opioid use disorder [OUD] has reached epidemic proportions with an estimated 2 million Americans currently having a prescription OUD and over 12 million reporting a history of opioid misuse.^{1,2} OUD is defined as a pattern of opioid use leading to clinically significant impairment and is diagnosed using criteria in the Diagnostic and Statistical Manual of Mental Disorders.³ As opioid prescribing has risen, the number of OUD deaths has nearly quadrupled.^{4,5} OUD inpatient hospital stays rose 64.1% in the past decade, a 5.7% annual growth rate.⁶ In response to this epidemic, the Center for Disease Control recently published guidelines on the management of chronic non-cancer pain, reserving prescription opioids only for those where benefits outweigh the risks.^{7,8}

Inflammatory bowel disease [IBD] is a relapsing-remitting chronic disease requiring regular access to health care. Patients with IBD are frequently prescribed opioids and are therefore at risk for OUD-related diagnoses.⁹ Given that abdominal pain is prevalent in IBD and patients often require procedures or surgical interventions, adequate pain control can be challenging. Furthermore, other pain-related diagnoses such as irritable bowel syndrome, ankylosing spondylitis, and peripheral arthritis can co-exist in IBD and can cause further debilitation. Accompanying psychosocial disorders may put these patients at additional risk for OUD.¹⁰

An estimated 17% of IBD patients report opioid use and two-thirds of those have associated misuse behaviour.¹¹⁻¹³ A recent study by Burr *et al.* evaluated the trend in opioid prescribing using a population-based database of IBD patients in the UK.¹⁴ Opioid prescriptions increased steadily over the study period, and heavy use was associated with an increase in all-cause mortality.¹⁴ We aimed to determine the prevalence and trends associated with OUD among hospitalised IBD patients, using a US nationally representative sample. We hypothesised a prevalence of OUD among hospitalised IBD patients greater than 1%, presuming a prevalence higher than the national prevalence estimate in the general population of 0.8%.¹⁵

2. Methods

A retrospective cross-sectional observational study was performed using Nationwide Inpatient Sample [NIS] data from 2005 to 2014. NIS is the largest all-payer inpatient database in the USA. It is funded by the US Agency for Healthcare Research and Quality as part of the Healthcare Cost and Utilisation Project [HCUP]. NIS includes discharge visit-level information including diagnoses, visit-related characteristics, and healthcare utilisation data.¹⁶ The unit of analysis for inpatient data is the hospital discharge, and a person who is readmitted will be counted for each admission as for a separate inpatient stay. The data were weighted to represent national estimates.¹⁷

The primary objective was to describe the prevalence and annual trends in OUD among the hospitalised IBD population. Secondary objectives included: 1) identifying predictors of OUD in IBD; and 2) determining visit-level outcomes associated with OUD in the hospitalised IBD population, specifically length of stay and IBD-related surgery.

IBD inpatient stays were identified using any discharge diagnosis of either Crohn's disease (International Classification of Diseases, Ninth Revision, Clinical Modification code [ICD-9-CM] 555.x) or ulcerative colitis [ICD-9-CM code 556.x].^{18,19} Discharges with an associated OUD diagnosis were identified using a schema previously described in an HCUP statistical brief, containing ICD-9-CM codes 304.00–304.02, 304.70–304.72, 305.50–305.52, 965.00–965.02, 965.09, 970.1, E850.0–850.2, E935.0–935.2, and E940.1.⁶

These ICD-9-CM codes represent active prescription and illicit opioid misuse and are further defined in [Supplementary Table 1](#), available as Supplementary data at [ECCO-JCC online](#). Patients younger than 18 years, older than 100 years, and those with indeterminate IBD [defined as a diagnosis of both ulcerative colitis and Crohn's disease within the same encounter] were excluded. Patients older than 100 years were excluded in compliance with the HCUP data use agreement requiring privacy protection against individual identification, which may be uncovered when reporting on characteristics of patients at the extremes of age.^{20,21}

Visit- and patient-level characteristics including age, gender, IBD type, primary payer [Medicare, Medicaid, Private, Uninsured, or other], US region [Northeast, Midwest, South, and West], a primary diagnosis of an IBD-related complication, and psychiatric comorbidities [mood disorder, anxiety and substance abuse] were collected. A primary diagnosis of an IBD-related complication was defined by ICD-9-CM code using a previously described schema which includes nine major complications [fistulising disease or intra-abdominal abscess, bowel obstruction, stricturing disease, haematochezia, malnutrition, anaemia, perianal disease, hypovolaemia, or electrolyte abnormality].^{18,22} Descriptive statistics were reported using means and standard deviation for continuous variables and frequency and percentages for categorical variables. Year-to-year trends in OUD-associated inpatient stays were analysed. A multivariable logistic regression analysis was performed to determine factors associated with having an OUD-related diagnosis; covariates associated with having an OUD-related diagnosis with a $p < 0.05$ on univariable analysis were retained in the multivariable model.

Health care utilisation was reported using length-of-stay measures. A multivariable linear regression model was constructed to measure the association between length of stay in days and having an OUD-related diagnosis. Variables controlling for length of stay were chosen *a priori* and included IBD type, in-hospital mortality, discharge against medical advice, IBD-related surgery, comorbid conditions, and Elixhauser comorbidity index.²³⁻²⁹ A comorbid condition was defined as one of a composite of visit-associated diagnoses of venous thromboembolism, pneumonia, sepsis, *Clostridium difficile* infection, blood transfusion requirement, and total parenteral or enteral nutrition. IBD-related surgery was defined using a composite of ICD-9-CM codes for small bowel and colorectal resections.³⁰ These and other ICD-9-CM codes are available in [Supplementary Table 1](#). A subgroup analysis of length of stay was performed for IBD-related surgical stays versus other inpatient stays. All statistical analyses were performed using STATA version 14.0 [Stata Corp, College Station, TX]. The study protocol was reviewed by the institutional review board and deemed exempt [IRB #1708018502].

3. Results

A total of 2 596 790 weighted adult discharges with any diagnosis of IBD were identified [[Figure 1](#)]. After excluding patients older than 100 years and those with diagnoses of both Crohn's disease and ulcerative colitis, the study population included a total of 2 585 174 weighted discharges: 36.4% had ulcerative colitis, 63.6% had Crohn's disease, and 7.5% of discharges were for a primary diagnosis of an IBD-related complication. Further baseline characteristics are reported in [Table 1](#).

Overall, 2.2% of IBD-related inpatient stays also had an OUD-related diagnosis, with an 8.8% average annual increase in IBD-related inpatient stays with an OUD-related diagnosis from 2005 to 2014 [$p < 0.001$] [[Figure 2](#)]. In univariable analysis, IBD patients

with OUD-associated inpatient stays were more likely to have Crohn's disease, to be Medicaid beneficiaries or uninsured, to be hospitalised in the West, and to have comorbid psychiatric disease, and were less likely to be admitted with a primary IBD-related complication [Table 1]. The association between individual IBD-related

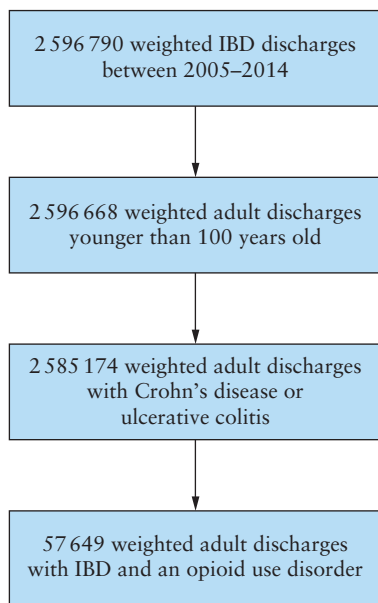


Figure 1. Flow diagram of study population after inclusion and exclusion criteria applied.

complications and OUD are reported in [Supplementary Table 2](#), available as Supplementary data at *ECCO-JCC* online. In multivariable analysis, Crohn's disease, public payer [Medicare or Medicaid], lack of insurance, and psychiatric comorbidities continued to be associated with a higher likelihood of OUD among IBD inpatient stays, whereas a diagnosis of a primary IBD-related complication was associated with a lower likelihood of an OUD inpatient stay, after controlling for region [Table 1].

IBD-related inpatient stays with an OUD-related diagnosis were associated with a 0.84 day [95% CI 0.71, 0.97] longer length of stay as compared with other IBD-related inpatient stays, after controlling for Elixhauser comorbidity index, IBD-related surgery, in-hospital death, discharge against medical advice, presence of an associated comorbid condition, and IBD type [Figure 3]. Having an OUD-related diagnosis was associated with a length of stay for surgical discharges increased by 2.79 days [95% CI 1.44, 4.14], and 0.71 days [95% CI 0.59, 0.82] for non-surgical discharges [Figure 3]. Hospitalisations involving an IBD-related surgery were less likely to be associated with an OUD on univariable analysis (unadjusted odds ratio [OR] 0.56, 95% CI 0.52, 0.61) and when controlling for age, IBD type, enteral or parenteral nutrition, and blood transfusion [Supplementary Figure 1, available as Supplementary data at *ECCO-JCC* online].

4. Discussion

Excessive opioid prescribing is one of many root causes of the opioid epidemic in the USA.³¹ The published literature has demonstrated an association between prescribing opioids and increased morbidity and mortality among IBD patients, but these studies have focused

Table 1. Patient- and visit-level characteristics among inflammatory bowel disease patients, associated with opioid use disorder, using univariable and multivariable regression analysis.

Variable	Overall	Opioid-use disorder	No opioid-use disorder	<i>p</i> -Value	Unadjusted OR	95% Confidence interval	Adjusted OR	95% Confidence interval
Inflammatory bowel disease type				<0.001				
Ulcerative colitis	36.4%	24.0%	36.6%		ref	ref	ref	ref
Crohn's disease	63.6%	76.0%	63.4%		1.83	1.75, 1.91	1.69	1.61, 1.77
Primary payer				<0.001				
Medicare	38.0%	34.5%	38.1%		1.29	1.23, 1.35	1.18	1.13, 1.24
Medicaid	11.3%	23.9%	11.0%		3.09	2.94, 3.25	2.42	2.29, 2.55
Private	41.8%	29.6%	42.0%		ref	ref	ref	ref
Uninsured	5.5%	8.3%	5.5%		2.15	2.00, 2.31	2.09	1.94, 2.26
Other	3.4%	3.7%	3.4%	1.55	1.40, 1.71	1.43	1.28, 1.58	
Region				<0.001				
Northeast	22.3%	23.1%	22.3%		ref	ref	ref	ref
Midwest	25.6%	22.1%	25.6%		0.83	0.79, 0.88	0.77	0.73, 0.81
South	35.5%	32.6%	35.6%		0.88	0.84, 0.93	0.84	0.79, 0.88
West	16.7%	22.2%	16.5%	1.29	1.22, 1.37	1.33	1.26, 1.41	
Primary IBD-related complication	7.5%	5.3%	7.5%	<0.001	0.69	0.64, 0.75	0.69	0.63, 0.75
Psychiatric disorder								
Mood disorder	17.1%	42.6%	16.5%	<0.001	3.74	3.60, 3.88	3.06	2.93, 3.19
Anxiety	9.2%	22.2%	8.9%	<0.001	2.91	2.78, 3.04	1.87	1.78, 1.96
Schizophrenia	1.3%	2.9%	1.2%	<0.001	2.42	2.17, 2.71	1.61	1.43, 1.81

IBD, inflammatory bowel disease; OR, odds ratio

on the peri-surgical period.^{32,33} However, outcomes such as overdose deaths are more closely associated with OUD than opioid prescribing alone.⁴ Therefore it is critical to investigate OUD in its own right, as opposed to simple post-surgical opioid use. This study focused on IBD patients with a diagnosis of OUD.

Our study demonstrates that OUD-related diagnoses are prevalent among more than 2% of IBD inpatient stays. These OUD estimates for IBD inpatients are higher than the numbers published for the overall inpatient population. Previous studies report a prevalence of OUD of 224.6 inpatient stays per 100 000 in the general

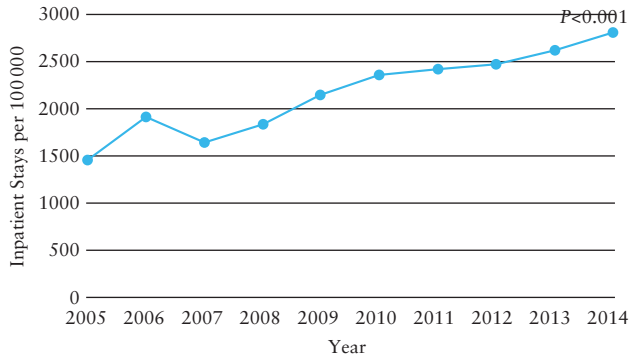


Figure 2. Trends in inflammatory bowel disease patients discharged with an associated opioid-use diagnosis.

population.⁶ This is also higher than outpatient population estimates of OUD, with a reported prevalence of 0.8%.¹⁵ Additionally, the rising trend in OUD-related diagnoses among inpatient hospitalisations is evident not only in the general population, but also in the IBD population specifically.^{13,34–36} Increasing provider awareness of OUD may contribute to rising OUD trends, but its overall influence is likely small, as studies have demonstrated that OUD remains vastly under-recognised.³⁷

Patients with IBD are at risk for opioid misuse, and this is apparent in the higher than average proportion of OUD-related diagnoses among those with inpatient IBD stays.⁶ Risk factors for OUD can be targeted to identify IBD patients who might benefit from screening for OUD or a review of their opioid prescriptions. We found that Crohn’s disease accounts for more OUD-related discharges than ulcerative colitis [Table 1]. The susceptibility of Crohn’s disease patients to opioid misuse has been reported in a systematic review and is thought to be related to the higher frequency of pain and need for more frequent surgery.¹¹ On the other hand, IBD-related complications and hospitalisations involving an IBD-related surgery were less likely to be associated with OUD diagnoses, possibly secondary to under-recognition of OUD in the setting of severe active disease.³⁷

Further, this study reveals a higher prevalence of OUD-related diagnoses in IBD patients with public payer insurance or who are uninsured. This is consistent with previous findings in other populations that demonstrate a higher rate of opioid use among Medicaid and Medicare enrollees.^{6,31,34,38–40} Given the inability to determine

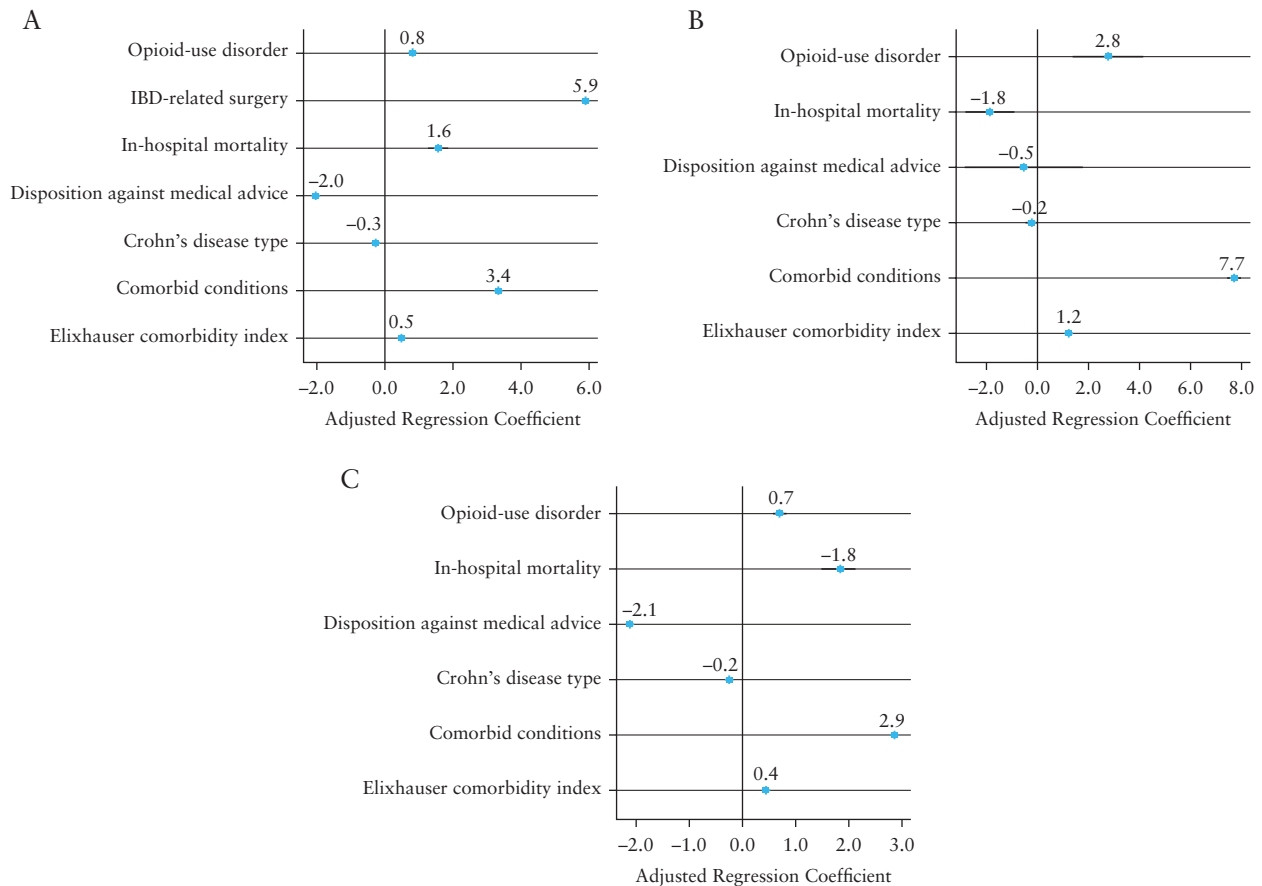


Figure 3. Multivariable model describing the association between length of stay [in days] and opioid use disorder, controlling for *a priori* covariates. A) All inflammatory bowel disease discharges; B) Subgroup of patients undergoing inflammatory bowel disease [IBD]-related surgery; C) subgroup of patients not undergoing an IBD-related surgery.

reasons for Medicaid eligibility in this dataset, it is unclear whether patients with OUD-related diagnoses were more likely to be Medicaid-insured as a result of a disability resulting from chronic pain and substance use disorder.

We also found a strong association between psychiatric disorders and opioid-related diagnoses in IBD hospitalised patients, particularly comorbid mood disorder, anxiety, and schizophrenia. Mood disorders are known to be associated with greater IBD care use and OUD.^{15,41,42} In a single-centre retrospective study of opioid misuse among IBD patients, Crocker *et al.* report 20% chronic narcotic use, with depression and anxiety as two independent predictors of misuse.^{15,43}

OUD-related diagnoses were also independently associated with longer length of stay that was particularly marked in the surgical subgroup of patients. A possible explanation of this could be due to more difficulty controlling pain or prolonged ileus from post-surgical opioid requirements. Additionally, patients with OUD are more prone to complications such as respiratory infections or to have co-occurring psychiatric diagnoses that complicate discharge, although we controlled for pneumonia and mood disorders in our multivariable model.⁴⁴

This study has several limitations. Importantly, because OUD is underdiagnosed, and our data were for inpatient stays, this study likely under-represents OUD among IBD patients.³⁷ Additional factors which could be associated with OUD, such as surgical history, personality traits, family history, and history of substance use, could not be evaluated using this dataset.^{8,45} Further, as an administrative database, patient identification is limited to ICD-9-CM billing codes which are prone to selection bias. Nonetheless, the ICD-9-CM codes for ulcerative colitis and Crohn's disease are well validated.^{18,22} Additionally, as NIS provides visit-level rather than patient-level data, we cannot account for longitudinal follow-up over time or post-discharge outcomes, such as readmissions. This could potentially lead to over-representation of patients who are prone to readmission. One study using HCUP data describes an association between opioid dependence and 30-day readmission in an IBD cohort with an odds ratio of 1.40 [95% CI 1.06, 1.86], but further exploration of the strength of this association is warranted.⁴⁶

This study also has several strengths. We evaluate the role of OUD on a population level using a large sample size, allowing for generalisability. Though limited by unforeseen confounders, we use multivariable models to control for confounding. Additionally, we specifically identify patients with a billable OUD diagnosis. This allows us to focus on identified OUD disorder which accounts for 5–25% of patients receiving prescription opioids.² Though OUD is likely under-recognized and underdiagnosed, this differentiates the present study from others that focus on frequency of opioid prescriptions as a marker of opioid misuse or dependence, which is difficult to differentiate from treatment of chronic pain or narcotic diversion, using large datasets.

There has been a recent rise in efforts to bring attention, funding and improved access to OUD treatment. However, to provide high-value interventions, the scope of OUD needs to first be demonstrated. OUD is prevalent among hospitalised IBD patients. Whereas it is important to focus on recognizing pain early in the disease process, and to target inflammation to change the natural history of IBD, we might also consider targeting patients at risk for OUD early in their disease course, substituting opioid alternatives and teaching coping mechanisms.¹ For those with identified OUD, treatment should be initiated without stigma. Where risk factors such as Crohn's disease type and psychiatric comorbidities have been identified, a validated predictive tool should be developed. Patients with IBD and OUD are

at high risk for greater health care utilisation and need to be targeted for preventive strategies.

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Conflict of Interest

ES has received grant/research support from Abbott Laboratories [AbbVie], AstraZeneca, Janssen Research & Development, and Pfizer, and serves as a consultant to AbbVie, Janssen Pharmaceutical, and Takeda Pharmaceuticals. The other authors have no relevant conflicts of interest to disclose.

Author Contributions

SC-M, RR, SG, and CC were involved in the study concept and design, data management, statistical analysis and interpretation of data, drafting of manuscript, and critical revisions. In addition, SC-M and CC were involved in study supervision. ES, RR, AW, SS, and BS were involved in interpretation of data and critical revisions. All authors approved the final version of the article, including the authorship list. Preliminary results were presented at the Crohn's Colitis Congress, Las Vegas, NV, in January 2018.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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