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Analysis of the clinical indications for opiate use in inflammatory bowel disease

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Background/Aims: Opiate use for inflammatory bowel disease (IBD), particularly high-dose (HD) use, is associated with increased mortality. It's assumed that opiate use is directly related to IBD-related complaints, although this hasn't been well defined. Our goal was to determine the indications for opiate use as a first step in developing strategies to prevent or decrease opiate use. **Methods:** A retrospective cohort was formed of adults who were diagnosed with IBD and for whom outpatient evaluations from 2009 to 2014 were documented. Opiate use was defined if opiates were prescribed for a minimum of 30 days over a 365-day period. Individual chart notes were then reviewed to determine the clinical indication(s) for low-dose (LD) and HD opiate use. **Results:** After a search of the electronic records of 1,109,277 patients, 3,226 patients with IBD were found. One hundred four patients were identified as opiate users, including 65 patients with Crohn's and 39 with ulcerative colitis; a total of 134 indications were available for these patients. IBD-related complaints accounted for 49.25% of the opiate indications, with abdominal pain (23.13%) being the most common. Overall, opiate use for IBD-related complaints (81.40% vs. 50.82%; *P*=0.0014) and abdominal pain (44.19% vs. 19.67%; *P*=0.0071) was more common among HD than among LD. **Conclusions:** Our findings show that most IBD patients using opiates, particularly HD users, used opiates for IBD-related complaints. Future research will need to determine the degree to which these complaints are related to disease activity and to formulate non-opiate pain management strategies for patients with both active and inactive IBD. **(Intest Res 2017;15:83-89)**

Key Words: Inflammatory bowel disease; Crohn disease; Colitis, ulcerative; Opiates; Narcotics

INTRODUCTION

Inflammatory bowel disease (IBD) is characterized by spontaneous or chronic intestinal inflammation. The two major types of IBD are UC, which is limited to the colon, and CD, which can affect any segment of the gastrointestinal tract. Common disease manifestations include abdominal pain, diarrhea, bleeding, and weight loss. Extraintestinal manifestations of IBD are also common and can involve nearly any organ system, but they most commonly affect the joints, skin, and eyes. Apart from primary bowel complaints, extraintestinal manifestations may lead to loss of function and pain, posing additional challenges to physicians treating these patients.

The primary approach to managing IBD-related complaints is treatment of the disease itself. Although the more widespread use of immune modulators and newer biologic therapies has improved response rates and prevented disease-related complications,[1-4] several patients still do not respond to treatment, lose response, or present with complications that are beyond the scope of the available medical therapies. In cases when IBD-directed medical therapies fail, it is often necessary to control patient complaints with symptom-directed medications. Because pain is such a

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prominent component of IBD, pain management and preserving quality of life are common challenges in treating patients with IBD.

IBD pain management is unfortunately complicated by evidence that commonly used analgesic medications such as NSAIDs may aggravate the disease.[5-7] Further, in addition to the well-known risk of dependence, it has long been a concern that opiates may impact IBD outcomes by either masking the signs of disease activity through their analgesic/anti-diarrheal effect or mimicking disease activity through their common side effects, such as nausea, vomiting, and altered intestinal motility with worsening abdominal pain. Although there is no direct evidence of exacerbation of IBD by opiates, recent reports have clearly demonstrated the association between opiate use and negative clinical outcomes in the IBD population.

The recent Crohn's therapy, resource, evaluation, and assessment tool (TREAT) registry update, which prospectively followed 6,273 CD patients for a mean duration of 5.2 years, demonstrated an association between opiate use and an increased risk of death in the CD population (hazard ratio [HR], 1.79; 95% CI, 1.29–2.48; P<0.001);[8] this finding is similar to the findings for corticosteroid use (HR, 2.14; 95% CI, 1.55–2.95; P<0.001).

More recently, a retrospective case/control analysis of the large Manitoba IBD database of 4,217 subjects (1,996 CD and 2,221 UC patients) over a median review period of 6.5 years also showed an increased risk of mortality associated specifically with high-dose (HD) opiate use, which was defined as a morphine equivalent dose of >50 mg/day (HR, 2.82; 95% CI, 1.58–5.02).[9] There was no increase in mortality related to low-dose (LD) opiate use, (HR, 1.33; 95% CI, 0.98–1.83). The study also showed that 5% of individuals with IBD started using opiates heavily within 10 years of diagnosis. The authors also showed that patients IBD were more than twice as likely to be opiate users as compared to non-IBD controls. The data suggested that the link between opiate use and an increase in mortality rate was related to greater disease severity, rather than to the direct harmful effect of opiates. Unfortunately, none of the studies provided information on disease activity that could be used to determine the direct association of both opiate use and/or mortality with IBD severity, nor did they specifically link opiate use with IBD-related complaints.

Although there is no information on the harmful effects of opiates in IBD patients, it is clear that opiate use is more prevalent among the IBD population than among the general community, and it is associated with an increased mortality rate. While it is likely that opiate use among IBD patients is largely driven by IBD-related complaints, there is limited information on the indications for opiate use in IBD patients. We aimed to characterize the indications for opiate use as a first step in formulating strategies to prevent or decrease opiate use among IBD patients.

METHODS

1. Study Design

1) Subjects

We formed a retrospective cohort of outpatients who visited the Northwell Health System. The health system coverage area includes over 10 million people, mainly from the New York metropolitan area. Data from January 1, 2009 to November 10, 2014 was collected from Allscripts, the outpatient electronic medical records (EMR) system. All adult patients with IBD who were >18 years old were identified by an International Classification of Disease (ICD-9) diagnostic code prefix of 555 for CD or 556 for UC. Patients with IBD were then defined as opiate users if they had a documented or electronically ordered opiate prescription for at least 30 days during the study period. The patients identified as opiate users were then further sub-categorized as either LD or HD users. The opiate dose was converted to morphine equivalents by using standard conversion formulas (Supplementary Table 1). HD use was defined as a morphine equivalent dose of >50 mg/day for at least a 30-day period, and doses that were below this cutoff amount were defined as LD. The cutoff was set at 50 mg because an increase in morbidity and mortality has been observed with opiate use above this threshold.[10,11]

2) Opiate Use Record

After identifying the IBD patients, each visit record corresponding to an opiate prescription order or documentation of use was analyzed for indications for opiate use. First, indications for opiate use were defined by an ICD-9 code in the EMR that linked the prescription order to a diagnosis or complaint. Opiate use could be linked to more than one diagnosis or complaint. Second, the medical provider chart notes corresponding to an opiate prescription order or documentation of use were reviewed to determine additional indications for opiate use. Patients were excluded if no clinical visit notes written by medical providers were available in the EMR system. If a patient had records of multiple clinical visits with documented opiate prescriptions, only the dose and indication(s) recorded in the clinical notes for the

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first visit were used for the main analysis. Additionally, usage of other IBD medications within 60 days of the opiate prescription was documented and analyzed. The medication categories were as follows: aminosalicylates, corticosteroids, immunomodulators, or biologics. Aminosalicylates included sulfasalazine and mesalamine (5-aminosalicylic acid) compounds taken orally, as enemas, or as suppositories. Immunomodulators included azathioprine, 6-mercaptopurine cyclosporine, tacrolimus, and methotrexate. Biologics included adalimumab, certolizumab, golimumab, infliximab, and vedolizumab. The study was approved by the Northwell Hofstra School of Medicine Institutional Review Board.

2. Statistical Analysis

Structured chart reviews were performed for patients with IBD and documented opiate use. Observational analysis was used to compare data between the LD and HD opiate users. IBD- and non-IBD-related issues were grouped by opiate use categories. The cumulative number of complaints/diagnoses cited exceeded the number of patients; therefore, two separate analyses, one of the clinical complaints and another of the patients, were conducted. Statistical significance was determine by using Fisher exact test, and continuous variables were expressed as means±SD.

RESULTS

1. Patients' Characteristics

The cohort of active patients in Allscripts from January 1, 2009 to November 1, 2014 included 1,109,277 subjects, of which 3,226 were diagnosed with IBD. A total of 111 patients were identified as opiate users. Of these, seven were excluded from the analysis because the opiate dose was not documented. Thus, 65 (62.5%) patients with CD and 39 (37.5%)

Table 1. Demographics Based on Opiate Use

Variable	Total opiate use	Low-dose opiate use	High-dose opiate use	*P*-value[a]
No. of patients	104 (100.00)	61 (58.65)	43 (41.34)	
Sex				0.5306
Male	47 (45.19)	26 (42.62)	21 (48.84)	
Female	57 (54.81)	35 (57.38)	22 (51.16)	
Age (yr)				0.0638
<60	65 (62.50)	43 (70.49)	22 (51.16)	
≥60	39 (37.50)	18 (29.51)	21 (48.84)	
CD	65 (62.5)	40 (65.57)	25 (58.14)	0.9590
UC	39 (37.5)	21 (34.43)	18 (41.86)	-

Values are presented as number (%).
[a]*P*-values for low-dose opiate use versus high-dose opiate use.

Table 2. IBD Medication Use

Medication	Total opiate use	Low-dose opiate use	High-dose opiate use	*P*-value[a]
Aminosalicylates[b]	22 (21.15)	16 (26.23)	6 (13.95)	0.1312
Corticosteroids	15 (14.42)	4 (6.56)	11 (25.58)	0.0065
Immunomodulators[c]	12 (11.54)	3 (4.92)	9 (20.93)	0.0254
Biologics[d]	39 (37.50)	15 (24.59)	24 (55.81)	0.0012
More than one medication	14 (13.46)	3 (4.92)	11 (25.58)	0.0024
Using any IBD medication	74 (71.15)	35 (57.38)	39 (90.70)	0.0030

Values are presented as number (%).
[a]*P*-values for low-dose opiate use versus high-dose opiate use.
[b]Includes sulfasalazine and 5-aminosalicylic acid compounds taken orally, as enemas, or as suppositories.
[c]Includes azathioprine, cyclosporine, tacrolimus, and methotrexate.
[d]Includes adalimumab, certolizumab, golimumab, and infliximab.

with UC were included in the analysis. A majority of the opiate users were women (54.8%, *P*=0.53), and the mean age of the subjects was 55.0±8.6 years. There was no difference in the rate of LD or HD use among patients by age or IBD type, i.e., CD and UC (Table 1). While there was no difference in aminosalicylate usage between LD and HD users, the use of all other IBD medications was significantly higher among HD users. Overall, over 90% of HD opiate users were receiving some form of medical treatment for IBD (Table 2). There was no significant difference in sex or age between the CD and UC patients (Table 3). Only 11 patients had documented multiple opiate prescriptions, with the median being 5. A majority of these patients were HD users (55.56% vs. 44.44%, *P*=0.048), with most of them citing abdominal pain (54.54%) as an indication for opiate use.

2. Indications for Opiate Use

The 104 patients reported a total of 134 complaints linked to opiate use. An analysis by complaints of the entire IBD group, as well as the LD and HD user subgroups, revealed abdominal pain to be the most commonly cited complaint linked to opiate use, accounting for 23.13% of the reported indications for opiate use (Table 4). Abdominal pain was more common among HD users than LD users (30.16% vs. 16.90%), but the difference was not statistically significant (*P*=0.0693). IBD-related complaints accounted for approximately half of the documented indications for opiate usage, with these complaints being the most common among HD users (55.56%). Among the IBD-related complaints, diarrhea was a relatively uncommon indication, being cited only twice (1.49%). Further, patients who had undergone IBD-

Table 3. Comparison of the Demographics of the CD and UC Patients

Variable	CD	UC	*P*-value
No. of patients	65	39	-
Sex			0.1696
Male	26 (40.00)	21 (53.85)	
Female	39 (60.00)	18 (46.15)	
Age (yr)			0.8360
≤30	8 (12.31)	7 (17.95)	
31–45	13 (20.00)	6 (15.38)	
46–60	21 (32.31)	10 (25.64)	
61–75	15 (23.07)	11 (28.21)	
≥76	8 (12.31)	5 (12.82)	

Values are presented as number (%).

Table 4. Indications for Opiate Use: Complaint Analysis

Complaint	Total	Low-dose opiate use	High-dose opiate use	*P*-value[a]
Total	134[b]	71 (53)	63 (47)	-
Abdominal pain	31 (23.13)	12 (16.90)	19 (30.16)	0.0693
Perianal fistula/abscess	13 (9.70)	8 (11.27)	5 (7.94)	0.5155
Pain due to post-IBD surgery	9 (6.72)	1 (1.41)	8 (12.70)	0.0128
IBD-related arthritis	7 (5.22)	6 (8.45)	1 (1.59)	0.1198
Erythema nodosum, iritis, pyoderma gangrenosum	4 (2.99)	3 (4.23)	1 (1.59)	0.6220
Diarrhea	2 (1.49)	1 (1.41)	1 (1.41)	1.0000
Total IBD indications	66 (49.25)	31 (43.66)	35 (55.56)	0.1693
Pain due to post non-IBD surgery	4 (2.98)	3 (4.23)	1 (1.59)	0.6220
Osteoarthritis	18 (13.43)	11 (15.49)	7 (11.11)	0.4578
Kidney stones	7 (5.22)	6 (8.45)	1 (1.59)	0.1198
Back pain	10 (7.46)	6 (8.45)	4 (6.35)	0.7490
Other[c]	29 (21.64)	14 (19.72)	15 (23.81)	0.5660
Total non-IBD indications	68 (50.75)	40 (56.34)	28 (44.44)	0.1693

Values are presented as number (%).
[a]*P*-values for low-dose opiate use versus high-dose opiate use.
[b]Total number of complaints.
[c]Denotes a combination of non-IBD categories: chronic regional pain syndrome, cancer, chronic pelvic pain, opioid addiction, bone fractures, migraines, dysmenorrhea, shoulder pain, and giant cell arteritis.

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Table 5. Indications for Opiate Use: Patient Analysis

Indications for opiate use	Total opiate use (n=104)	Low-dose opiate use (n=61)	High-dose opiate use (n=43)	*P*-value[a]
Patients with abdominal pain	31 (29.81)	12 (19.67)	19 (44.19)	0.0071
Total patients with an IBD indication	66 (63.46)	31 (50.82)	35 (81.40)	0.0014

Values are presented as number (%).
[a]*P*-values for low-dose opiate use versus high-dose opiate use.

Table 6. Comparison of the Indications for Opiate Use between CD and UC Patients

Indication for opiate use	Total patients (n=104)	CD (n=65)	UC (n=39)	*P*-value[a]
Patients with abdominal pain	31 (29.81)	25 (38.46)	6 (15.38)	0.0127
Total patients with any IBD indication	66 (63.46)	47 (72.31)	19 (48.72)	0.0156

Values are presented as number (%).
[a]*P*-values for low-dose opiate use versus high-dose opiate use.

related surgeries were more likely to take a high dose of opioids (12.70% vs. 1.41%, *P*=0.0128). In addition, although perianal fistula or abscess accounted for only 9.7% of IBD-related complaints, of the 65 CD patients, perianal fistula or abscess was cited as an indication for opiate use for 13 patients (20%) and for five patients (20%) who were HD users.

Abdominal pain (44.19% vs. 19.67%, *P*=0.0071) and IBD-related complaints (81.40% vs. 50.82%, *P*=0.0014) were cited more commonly among HD than among LD users (Table 5). An analysis by disease revealed that abdominal pain (38.46% vs. 15.38%, *P*=0.0127) and IBD-related complaints (72.3% vs. 48.72%, *P*=0.0156) as an indication for opiate use were more common among CD than among UC patients (Table 6).

DISCUSSION

The analysis of our population-based cohort revealed the clinical indications for opiate use in patients with IBD. Opiate use for IBD has been associated with poor clinical outcomes. Although it was assumed that opiate use in the IBD population is related to IBD activity and its complications, our study is the first to directly establish this link. IBD-related complaints accounted for roughly half of the cited clinical indications for prescribing opiates in our IBD cohort as well as in the LD and HD opiate use subgroups. When analysis was conducted on a per-patient basis instead, it was found that almost two-thirds of the patients cited an IBD-related complaint as a reason for their opiate use, with this figure rising to 81% among the HD patients. The significantly higher use of IBD medications among HD users indirectly indicates that IBD activity or complaints could be the main factor influencing opiate use. Expectedly, abdominal pain was the most common indication for opiate use, particularly among CD patients, and was cited by almost half of the HD users. Perianal complaints were also commonly attributed to opiate use in the CD group. Notably, in contrast to traditional assumptions, diarrhea was rarely documented as an indication for opiate use by the prescribing physician or as relayed to the physician.

Other studies have examined the clinical features of IBD and opiate use, reporting important associations between IBD and co-morbid disease; however, they did not precisely define the indications for opiate use. Early work presented by Kaplan and Korelitz[12] from a single specialty IBD center noted a 30% risk of drug dependence among patients with IBD referred for psychiatric consultation. Edwards et al.,[13] utilizing an IBD database of 332 patients in Queensland Australia, studied patients with documented evidence of chronic opiate use over a period of 6 months for abdominal pain. After excluding patients with chronic active disease, diarrhea, and bowel obstruction, they identified 11 patients (10 with CD) who they defined as having "chronic narcotic misuse." Two patients were excluded from the final analysis because of incomplete data. Of the remaining nine patients, six had diagnosed psychiatric disorders, including depression, anxiety, anxiety with depression, bipolar illness, obsessive compulsive disorder, and personality disorder. Cross et al.[14] performed a retrospective review and case control analysis of 291 patients with CD followed over a 5-year period at the Medical College of Wisconsin's IBD Center. Similarly, patients who were prescribed opiates for diarrhea were excluded and those with active disease were included.

The authors identified 38 patients (13.1%) who were opiate users, and its use was associated with psychiatric illness as determined from the increased neuropsychiatric drug use of 37% as compared to 19% among non-opiate users (P=0.01). Opiate users had higher disease activity as measured by the Harvey Bradshaw Index (9.1 vs. 5.0, P<0.001), lower quality of life scores as measured by the Short Form Inflammatory Bowel Disease Questionnaire (44.2 vs. 51.6, P=0.04), higher rates of disability (15.4% vs. 3.6%, P=0.001), and longer disease duration (17.0 years vs. 12.9 years, P=0.03). Logistic regression analysis also showed that smoking was more common among narcotic users (OR, 2.8). In another retrospective case control analysis of patients at the Mayo Clinic, Hanson et al.[15] identified 361 patients with IBD who were opiate users. Their final analysis of 100 mixed IBD cases (78 CD and 22 UC) was limited to patients receiving opiates for IBD indications, thereby excluding 194 patients who were receiving opiates for non-IBD indications and 67 patients without a confirmed IBD diagnosis. Unlike the findings in our study, the study by Hanson et al.[15] suggests that, in most cases, opiate use among IBD patients is unrelated to the disease itself, although it is not certain if multiple complaints cited by a subject were addressed or what comprised the IBD-related complaints in the 100 patients analyzed. Depression (42% vs. 19%, P<0.001) and anxiety (19% vs. 7%, P=0.02) were again found to be more common among opiate users, along with a history of abuse (17% vs. 3%, P=0.006) and non-alcohol substance abuse (14% vs. 1%, P<0.001). In their larger population-based study, Targownik et al.[9] also observed an association between depression (HR, 2.22; 95% CI, 1.34–3.67) and substance abuse (HR, 4.05; 95% CI, 12.82–9.01) in HD opiate users, while acknowledging that their study design precluded the identification of precise indications for opiate use.

The main advantage of our study design was the use of population-based data available through the EMR system. After analyzing over 1.1 million subjects, we were able to identify 3,226 patients who had a diagnosis of IBD. While the IBD diagnosis was not validated by an additional review of the medical records, the observed prevalence of IBD of approximately 0.3% in our population was similar to the rate in the US population as a whole.[16,17] We were able to define opiate use in 3.4% of our IBD patients, and this figure is slightly lower than that observed by Targownik. Unlike in the Manitoba Health database, patients included in the Northwell Health EMR system commonly consult physicians outside of the health care system, which blinds our investigation to opiate prescription that are not recorded within the system; this likely resulted in underreporting of opiate use in our cohort. Additionally, since only a single complaint or diagnosis needs to be linked to a prescription order in the EMR system, it is possible that the total number of clinical complaints was underreported. This linkage of prescription orders to a complaint or diagnosis may have also biased the results by enabling physicians to avoid linking an opiate prescription to a complaint that is perceived to be an unacceptable indication, e.g., diarrhea. Additionally, the date of the IBD diagnosis is not recorded in the EMR system, and therefore it is possible that some opiate prescriptions could have ordered prior to a formal IBD diagnosis. Another significant limitation of our study, which is common for retrospective investigations, was our inability to correlate complaints with disease activity, disease location, or behavior. While the absence of objectively defined disease activity would not automatically imply that a complaint was unrelated to IBD, it would have provided additional important insight into the nature of pain experienced by our patients, i.e., how much of what we see may be treatable by addressing IBD activity itself, and how much pain is beyond the scope of disease directed therapy. Since it is well known that there is often a disconnect between IBD complaints and true inflammatory disease activity,[18-20] it is unlikely that increasing the scope or introducing new IBD-modifying therapies will suffice as alternatives for pain management.

Although opiate use in IBD has previously been associated with comorbidities such as smoking, substance abuse, and psychiatric diseases, the indications for use have been poorly defined. Our analysis of a non-referral center, population-based IBD cohort shows that IBD complaints, especially abdominal pain, are the most common indications for opiate use, particularly among HD users. While it is unknown if HD opiate use causes direct harm to patients, it should be assumed. Opiate use, irrespective of the reason, should be treated as a red flag, and physicians should thoroughly reevaluate cases to determine evidence of active disease and modify treatment accordingly. In cases where evidence of active disease is absent, early consultation with pain management specialists is recommended to help the patient limit or eliminate opiate use. Future research should address non-opiate pain management strategies for IBD-related pain along with an emphasis on early, highly effective IBD therapy to prevent the disease complications that would lead to opiate use.

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Supplementary Table 1. Oral Opioid Analgesic Equivalence Table[a]

Opioid	Ratio (opioid:morphine)
Morphine sulfate	1:1.00
Codeine phosphate	1:0.15
Oxycodone hydrochloride	1:1.50
Hydromorphone hydrochloride	1:5.00
Meperidine hydrochloride	1:0.10
Transdermal fentanyl	25 μg/h→1:97
	50 μg/h→1:202
	75 μg/h→1:292
	100 μg/h→1:382

[a]Adapted from Kahan M, et al. Can Fam Physician 2011;57:1257-1266.[21]