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Riggott, C., Fairbrass, K.M., Selinger, C.P. et al. (2 more authors) (2023) Impact of Opioid Use on the Natural History of Inflammatory Bowel Disease: Prospective Longitudinal Follow-up Study. Inflammatory Bowel Diseases. ISSN 1078-0998

https://doi.org/10.1093/ibd/izad256

Accepted for publication 3rd October 2023

TITLE PAGE

Title: Impact of Opioid Use on the Natural History of Inflammatory Bowel Disease: Prospective Longitudinal Follow-up Study.

Short Title: Opioids and IBD: Prospective Longitudinal Follow-up Study.

Summary: Of the 1029 patients with IBD in this study, opioid use exceeded 10%, and was associated with psychological co-morbidity and an increased risk of intestinal resection during longitudinal follow up, particularly when more potent formulations were used.

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Funding: None

Abbreviations:

CD	Crohn's disease
CI	confidence interval
HADS	hospital anxiety and depression scale
HBI	Harvey-Bradshaw index
HR	hazard ratio

IBD	inflammatory bowel disease
IBD-U	inflammatory bowel disease unclassified
IBS	irritable bowel syndrome
OR	odds ratio
PHQ	patient health questionnaire
SCCAI	simple clinical colitis activity index
UC	ulcerative colitis

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Key words: inflammatory bowel disease

opioids

prognosis

Conflict of interest: Christy Riggott: none. Keeley M. Fairbrass: none. Christian P. Selinger: has received unrestricted research grants from Warner Chilcott, Janssen, and AbbVie, has provided consultancy to Warner Chilcott, Dr Falk, AbbVie, Takeda, Fresenius Kabi, Galapagos, Arena, and Janssen, and had speaker arrangements with Warner Chilcott, Dr Falk, AbbVie, MSD, Pfizer, Celltrion, and Takeda. David J. Gracie: none. Alexander C. Ford: none.

Specific author contributions: KMF, DJG, and ACF conceived and drafted the study. KMF collected all data. CR and ACF analyzed and interpreted the data. CR and ACF drafted the manuscript. All authors contributed to and approved the final draft of the manuscript.

Guarantor: ACF is guarantor.

Word count: 3396

Background: Opioid use is increasingly prevalent amongst patients with inflammatory bowel disease (IBD), but whether opioids have deleterious effects, or their use is merely linked with more severe disease, is unclear.

Aims: To conduct a 12-month longitudinal follow-up study examining this issue.

Methods: We collected demographic, symptom, psychological, quality of life, and opioid use data at baseline and healthcare utilization and IBD outcomes via medical records review at 12 months. Characteristics of those using opioids and those who were not were compared, in addition to occurrence of flare, glucocorticosteroid prescription, escalation of therapy, hospitalization, or intestinal resection during longitudinal follow-up.

Results: Of 1029 eligible participants, 116 (11.3%) were taking opioids at baseline. Medium (odds ratio (OR) = 4.67; 95% confidence interval (CI) 1.61-13.6) or high (OR = 8.03; 95% CI 2.21-29.2) levels of somatoform symptom-reporting and use of antidepressants (OR = 2.54; 95% CI 1.34-4.84) or glucocorticosteroids (OR = 6.63; 95% CI 2.26-19.5) (p<0.01 for all analyses) were independently associated with opioid use. Following multivariate analysis, opioid users were significantly more likely to undergo intestinal resection (HR = 7.09; 95% CI 1.63 to 30.9, p=0.009), particularly when codeine or dihydrocodeine were excluded (HR = 42.9; 95% CI 3.36 to 548, p=0.004).

Conclusions: Opioid use in IBD is associated with psychological co-morbidity and increased risk of intestinal resection, particularly in stronger formulations. Future studies should stratify the risk of individual opioids, so that robust prescribing algorithms can be developed, and assess whether addressing psychological factors in routine IBD care could be an effective opioid avoidance strategy.

Key messages

- Persistent pain is experienced by up to 50% of patients with inflammatory bowel disease (IBD) and despite established gastrointestinal side effects, opioid use is becoming increasingly prevalent.
- Even when controlling for baseline data, including disease extent and phenotype, patients with IBD using opioids had an increased risk of intestinal resection. This risk increased further when weaker formulations were excluded from the analyses.
- Awareness of the specific risks that opioids pose to patients with IBD enables physicians to exert due caution when prescribing them, particularly in stronger formulations.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are the two main types of inflammatory bowel disease (IBD), characterized by recurrent inflammation of the gastrointestinal mucosa. They follow a chronic relapsing and remitting course with symptoms including diarrhea, hematochezia, and urgency. Abdominal pain is experienced by up to 70% of patients during flares of disease activity, which may be linked to underlying mucosal inflammation, extraintestinal manifestations of IBD, or disease complications including strictures, adhesions, or abscess formation.[1]

However, persistent abdominal pain is experienced by up to 50% of patients with quiescent IBD, suggesting that a simple linear relationship with disease activity does not explain the underlying etiology of pain in IBD completely.[2] Psychological factors may contribute to the development of visceral hypersensitivity, via complex gut-brain interactions.[2-6] Furthermore, up to one quarter of patients with IBD report symptoms compatible with irritable bowel syndrome (IBS), which is also characterized by abdominal pain.[7,8] Pain management in IBD may be complicated by gastrointestinal side effects of many available analgesics.[9] Non-steroidal anti-inflammatory drugs can potentiate mucosal injury, and opioids have an array of deleterious effects, including enteric dysmotility, hyperalgesia, and even narcotic bowel syndrome.[10] There are additional concerns that opioids may mask the symptoms of disease activity in IBD, precipitating complications such as toxic megacolon.[11]

Despite this, data suggest that between 70% and 90% of patients hospitalized due to IBD received opioids during their admission,[12,13] and it has been reported that one-in-five patients use them in the outpatient setting.[14] A recent UK based study reported a 20% increase in the dispensing of opioid prescriptions for patients with IBD between 1990 and

2013.[15] Factors associated with their use include female sex, psychological co-morbidity, increased disease severity, and prior gastrointestinal surgery.[12,14-18]

In light of the opioid crisis sweeping the United States, concerns are mounting regarding the use of opioids for non-cancer related pain.[19] Research in to the harmful effects of opioids in patients with IBD remains limited, but there is accumulating evidence that their use in IBD is associated with reduced quality of life, psychological co-morbidity,[16,20] increased healthcare utilization and risk of infection,[18,20,21] and premature all-cause mortality.[15,22] However, most studies have been conducted in the United States, which limits generalizability, and few studies detail type of opioid used.[17,22] In addition, opioid use may be associated with more active disease at baseline, making it difficult to determine if these outcomes are a direct consequence of opioids, or if opioid use is merely an indicator of more severe disease.[14] We conducted a 12-month prospective longitudinal follow-up study of patients in a secondary care setting, hypothesizing that use of opioids at baseline would be associated with worse disease outcomes including treatment escalation, hospitalization, intestinal resection, and all-cause mortality.

METHODS

Participants and Setting

Ambulatory patients aged ≥18 years with an established histological, endoscopic, or radiological diagnosis of CD, UC, or IBD unclassified (IBD-U) seen in outpatient clinics between 2017 and 2020 at Leeds Teaching Hospitals NHS Trust were sent invitations to participate by post. We are the sole provider of care for all these patients through the UK NHS. This study was nested within a longitudinal survey that aimed to examine the impact of the trajectories of symptoms of anxiety or depression on the natural history of IBD.[23] The invitation enabled access to an online patient information sheet and questionnaire, as well as a consent form, via a web-link with a personalized uniform resource locator. Paper versions of these documents were available, if preferred. Patients with an end ileostomy, colostomy, or ileo-anal pouch were excluded, due to difficulties in assessing clinical disease activity. We obtained approval for this longitudinal follow-up study from the Wales research ethics committee in February 2020 (REC ref: 20/WA/0044).

Data Collection and Synthesis

Demographic data, including sex, age, marital status, educational level, and lifestyle (tobacco and alcohol consumption) were recorded, as well as clinical disease activity, psychological health, quality of life, Rome IV IBS-type symptoms, and medication use at baseline. We assessed clinical disease using a modified Harvey-Bradshaw index (HBI) for Crohn's disease (CD), excluding the examination for abdominal mass,[24,25] and the simple clinical colitis activity index (SCCAI) for ulcerative colitis (UC).[26] We used a score of <5 to define remission for both, as recommended.[27,28] We used the hospital anxiety and depression scale (HADS) to screen for symptoms of anxiety or depression.[29] The total HADS scores

range from 0 to 21. We defined HADS-anxiety or depression scores as normal (score 0-7), borderline (8-10), or abnormal (≥11), as recommended.[29] Somatoform symptom-reporting data were collected using the patient health questionnaire-12 (PHQ-12),[30] which is derived from the PHQ-15.[31] Scores range from 0 to 24 and we characterized severity as high (total score ≥13), medium (8-12), low (4-7), or minimal (≤3). The PHQ-12 has been previously validated in other patients with chronic gastrointestinal symptoms.[30] In this study, the upper limit of the interquartile range in healthy people reached 13, hence our selection of this cut off to define high levels of somatoform symptoms. The median value in those with IBS was 8, hence our choice of this to define medium levels of somatoform symptoms. Quality of life was measured using the short inflammatory bowel disease (IBD) questionnaire (SIBDQ) health survey.[32] We assessed for presence of IBS-type symptoms using the Rome IV questionnaire,[33] which requires abdominal pain to be present on a weekly basis to meet criteria for Rome IV IBS. Finally, we collected data concerning current use of opioids at baseline, asking patients whether they were regularly using opioids for pain control, as well as current use of antidepressants at baseline.

Electronic medical records were reviewed for all participants by one investigator (KMF), who was blinded to the questionnaire data. IBD type (CD, UC, or IBD unclassified), extent and location of disease, prior IBD-related intestinal surgery, and current use of IBD-related medications (5-aminosalicylates, immunosuppressants, biologic therapies, or glucocorticosteroids) were collected. This investigator also recorded the occurrence of any of the following clinical outcomes during longitudinal follow-up for a minimum of 12 months, along with the date of their occurrence: flare of disease activity based on a physician's global assessment; glucocorticosteroid prescription; escalation of medical therapy due to uncontrolled IBD activity; hospitalization due to uncontrolled IBD activity; or intestinal resection due to uncontrolled IBD activity. Changes to medication without evidence of

uncontrolled IBD activity (e.g., based on the results of therapeutic drug monitoring), or surgery for isolated perianal CD, were not included as endpoints.

Statistical Analysis

We compared characteristics of those using opioids at baseline with those not using these drugs. For comparison of data between groups we used a Pearson's χ^2 test for categorical data and an independent samples *t*-test for continuous data. We performed multivariate logistic regression to assess for factors independently associated with opioid use at baseline, with results expressed as odds ratios (OR) with 95% confidence intervals (CI). To assess for an association between opioid use at baseline and each of the disease activity outcomes of interest (flare of disease activity, glucocorticosteroid prescription, escalation of therapy, hospitalization, or intestinal resection) during longitudinal follow-up we compared their rates between users and non-users. We also assessed for an association between opioid use and occurrence of composite outcomes, including one or more of the events of interest. We used a Pearson's χ^2 test for categorical data and univariate Cox regression analysis, with results of the latter expressed as hazard rations (HR) with 95% CIs. Factors independently associated with the development of each of these outcomes were determined by performing multivariate Cox regression analysis to control for all baseline characteristics, including prior intestinal resection, disease activity at baseline, self-report of a flare at baseline, and presence of Rome IV IBS-type symptoms at baseline, and were reported as HRs with 95% CIs. Due to multiple comparisons, we considered a 2-tailed *p* value of <0.01 as statistically significant for all analyses, which were performed using SPSS for Windows version 26.0.

RESULTS

In total, 4823 patients with IBD seen in the outpatient clinic between January 2017 and June 2020 were contacted. Of these, 1119 (23.2%) responded to the baseline questionnaire. However, 88 (7.9%) were ineligible due to either a stoma or ileo-anal pouch, and a further two (0.2%) individuals did not provide complete data regarding opioid use at baseline. This meant 1029 (92.0%) of 1119 responders (mean age 52.6 years (SD 16.9 years), 563 (54.7%) female, 459 (44.6%) CD) were eligible and provided baseline data. In total, 116 (11.3%) patients were taking opioids at baseline. These consisted of codeine in 70 (60.3%) patients, tramadol in 23 (19.8%) patients, dihydrocodeine in seven (6.0%) patients, oramorph in five (4.3%) patients, buprenorphine in four (3.4%) patients, fentanyl in three (2.6%) patients, morphine in three (2.6%) patients, and oxycodone in one (0.9%) patient. We included data from all patients in our primary analysis but, given that codeine and dihydrocodeine may be used as antidiarrheal agents by some patients with IBD, we excluded these two drugs in a sensitivity analysis.

Characteristics of Patients Using Opioids at Baseline

After univariate analysis, those reporting use of opioids at baseline were significantly more likely to be older, to have CD, to have had a previous intestinal resection, to report a flare at baseline, to exhibit clinical disease activity according to the Harvey-Bradshaw index (HBI) or simple clinical colitis activity index (SCCAI), to be taking antidepressants, to have abnormal hospital anxiety and depression scale (HADS)-anxiety or HADS-depression scores, to have higher somatoform symptom-reporting scores, and to report symptoms compatible with the Rome IV criteria for IBS (Table 1). They were significantly less likely to have reached a university or postgraduate level of education and reported significantly lower quality of life. After multivariate logistic regression controlling for all baseline data, factors

independently associated with use of opioids included use of antidepressants (OR = 2.54; 95% CI 1.34 to 4.84, p=0.004) or glucocorticosteroids (OR = 6.63; 95% CI 2.26 to 19.5, p=0.001), and exhibiting medium (OR = 4.67; 95% CI 1.61 to 13.6, p=0.005) or high (OR = 8.03; 95% CI 2.21 to 29.2, p=0.002) levels of somatoform symptom-reporting.

Clinical Outcomes of Patients According to Opioid Use

The use of opioids at baseline was significantly associated with intestinal resection during follow-up (HR = 4.44; 95% CI 1.64 to 12.0, p=0.003) (Table 2). After multivariate Cox regression analysis, controlling for all baseline data, those using opioids were significantly more likely to undergo intestinal resection (HR = 7.09; 95% CI 1.63 to 30.9, p=0.009) (Table 2 and Figure 1). This association persisted in multivariate Cox regression analysis when patients with a prior history of intestinal resection (HR = 8.16; 95% CI 1.32 to 50.3, p = 0.24) or patients self-reporting a current flare of disease activity (HR = 23.9; 95% CI 1.75 to 326, p = 0.17) were excluded from the analysis.

Clinical Outcomes of Patients According to Opioid Use Other Than Codeine or Dihydrocodeine

After excluding the 77 patients taking either codeine or dihydrocodeine, the significant association between use of opioids at baseline and intestinal resection (HR = 6.75; 95% CI 1.88 to 24.2, p=0.003) remained on univariate analysis (Table 3). After multivariate analysis, those using opioids other than codeine or dihydrocodeine were significantly more likely to undergo intestinal resection (HR = 42.9; 95% CI 3.36 to 548, p=0.004) (Table 3).

DISCUSSION

This prospective study has examined factors associated with opioid use in patients with IBD and the impact of their use on prognosis using objective markers of disease activity. The extent of opioid exposure is consistent with a recent multi-center audit of UK IBD patients.[34] Factors that were independently associated with opioid use included antidepressant or glucocorticosteroid prescription and higher levels of somatoform symptom-reporting. The use of opioids was significantly associated with intestinal resection during longitudinal follow-up in univariate analysis. After multivariate Cox regression controlling for all baseline data, use of opioids was associated with a seven times higher risk of intestinal resection. When we excluded patients with a prior history of intestinal resection, patients self-reporting a flare of disease activity at baseline, or patients taking codeine or dihydrocodeine, which may be used as antidiarrheal agents and are classed as weaker opioids by the British National Formulary,[35] similar results were observed. After multivariate Cox regression, use of opioids was still associated with intestinal resection during longitudinal follow-up, with a more than 30 times higher risk, although 95% CIs around this estimate were wide due to a smaller sample size, as more than 60% of the patients were taking these drugs.

Our study included a relatively large, unselected cohort of patients with IBD. This means the results are likely to be generalizable to patients seen in other secondary and tertiary IBD centers. The fact that enrollment was predominantly via personalized links to online questionnaires is likely to have reduced the likelihood of there being missing data among participants. We assessed the impact of opioid use on disease outcomes via blinded review of electronic medical records and this was undertaken by a single investigator, which is likely to have avoided any potential for inter-observer variation.

However, there are some limitations of this study. Although we are the sole provider of care for all these patients, we cannot exclude the possibility that a small number of patients

may have experienced one of the events of interest in another center, and these data would not have been capture by our review of electronic medical records. The sample size was large and rates of hospitalization and intestinal resection were numerically higher among those using opioids, but only one-in-four of those invited chose to participate, and the 12-month study duration resulted in relatively low event rates for these endpoints. Studies with longer follow-up will, therefore, be important. There were fewer patients taking strong opioids, meaning that making definitive conclusions regarding the impact of these drugs on the prognosis of IBD are inappropriate. We did not assess for other health conditions, or extra-intestinal manifestations of IBD, which may be related to opioid use, for example inflammatory or degenerative joint disease. Nevertheless, the number of extra-intestinal manifestations currently experienced is included within both the HBI and SCCAI, and disease activity at baseline was controlled for in multivariate analysis. Likewise, we did not confirm the indication for opioid use, or the exact drug, from the medical records but relied on patient-report. Nor did we assess whether prescriptions for opioids had been filled or whether patients were adherent. Only 23% of patients we contacted responded to our questionnaire, which may have introduced volunteer bias. The study was nested within a longitudinal follow-up study assessing the impact of trajectories of symptoms of anxiety or depression on the natural history of IBD.[23] However, as the rates of reporting of symptoms of anxiety or depression were similar to those reported in the literature among patients with IBD, we suspect volunteer bias on this basis is unlikely.[36] In addition, opioids and their impact on the natural history of IBD were not mentioned at all in the participant information sheet. We, therefore, feel this is also unlikely to have had a huge impact on our results. We could not assess the characteristics of non-responders to our baseline questionnaire. This means that we cannot exclude the potential for volunteer bias among patients enrolled, with those using opioids more likely to participate. However, as this was not the main aim of this

study,[23] we suspect this is unlikely. Finally, we did not use objective markers of active disease, such as endoscopic assessment, fecal calprotectin, or C-reactive protein, to assess IBD activity at baseline. Instead, we used patient-reported clinical disease activity scores. As recruitment took place during the COVID-19 pandemic, persuading patients with IBD to attend a face-to-face appointment to provide stool or blood for analysis was undesirable and performing an endoscopic assessment in over 1000 patients would have been impractical. This could have led to residual confounding if mucosal inflammation, rather than disease activity scores, is linked to opioid prescribing, although we are not aware of any data to support that. However, this will not have affected our findings during longitudinal follow-up, as these were based on a blinded assessment of medical records.

The prevalence of opioid use among patients in this study was more than double that of the general population in the UK,[37] and is in line with findings from other studies of patients with IBD.[17,34] In our study, opioid users were three times more likely to be taking antidepressants than non-opioid users, which is comparable with other studies examining opioid use in IBD.[13-15] Although a recent meta-analysis by Niccum *et al.* suggested depression is independently associated with opioid use,[17] psychological co-morbidity is more prevalent in patients with IBD than among the general population.[36] The relationship between depression or prescribed antidepressants and increased opioid use is, therefore, probably more complex than a simple cause and effect relationship, with opioid use in this subgroup of patients perhaps a marker for a higher burden of chronic pain and co-existing psychological co-morbidity.[8,22] In addition, higher levels of somatoform symptom-reporting in patients taking opioids was also demonstrated in our study. This is, perhaps, unsurprising given that pain is often a symptom of somatoform disorders, is linked with irritable bowel syndrome, which co-exists in around 25% of patients with IBD,[7,8] and that other chronic painful conditions are common in patients with IBD. Furthermore, health care professionals may use

antidepressants like amitriptyline to manage irritable bowel syndrome-type symptoms occurring in some patients with IBD. Along with antidepressant use, the higher level of somatoform symptom reporting associated with opioid use in this study underscores the importance of addressing psychological factors in IBD, which is not considered by the current management paradigm in most countries.[4]

The four times higher risk of intestinal resection in opioid users identified in this study is noteworthy, as intestinal resection is a significant cause of morbidity in IBD,[38] and there is limited evidence in the literature relating to this particular association. One study by Wren *et al.* found that long-term use of opioids was associated with more gastrointestinal surgeries in adolescents,[14] and in a retrospective cohort study of adult patients with IBD those undergoing a colectomy were more likely to have used opioids for >60 days in the preceding year.[20] Whether the higher risk of intestinal resection is causally related to opioid exposure or whether patients requiring opioid analgesia represent a more severe phenotype requires further study, although disease activity and prior intestinal resection were controlled for in our multivariate analysis.

Pain management represents a substantial unmet need for patients with IBD, however, and pain is associated with lower health-related quality of life and functional disability.[1,6] This makes a blanket recommendation for clinicians to cease the prescriptions of all opioids in patients with IBD unrealistic, particularly in view of the limited alternative analgesics available to manage pain in these patients.[9] However, altering prescribing practices may be achievable with more detailed knowledge of effects of individual opioids on outcomes in IBD. Studies in non-IBD populations demonstrate that stronger opioid formulations are associated with increased morbidity and mortality compared with weaker formulations.[39] In one study that examined the association between weak and strong opioid formulations and mortality in IBD, stronger formulations were associated with an increased mortality.[15] Our

study examined the effects of different opioid formulations on specific IBD outcomes, demonstrating that effect sizes for intestinal resection were even higher when individuals using codeine or dihydrocodeine, which may be taken for their anti-diarrheal effects, were excluded from the analysis. This suggests that it is other, stronger, opioids that are associated with worse disease outcomes in IBD. However, further large-scale prospective studies will be needed to confirm our findings. This could help stratify individual risk of these drugs on disease outcomes, allowing more nuanced recommendations on their prescribing to be made.

In summary, the high prevalence of opioid use in patients with IBD, coupled with its association with increased healthcare utilization, intestinal resection, and all-cause mortality means that it is imperative that prescribers understand the risks associated with use of these drugs in a potentially vulnerable group of patients. As seen in other studies, we demonstrated that psychological co-morbidity was associated with opioid use in patients with IBD, suggesting that addressing psychological factors in routine IBD care is essential going forward. This may be one strategy to reduce opioid prescribing. In addition, there may be a prominent association between worsening disease outcomes and the use of certain, stronger, opioid formulations, which may be useful to guide future prescribing recommendations, and warrants further research.

ACKNOWLEDGEMENTS

We are grateful to the patients who took the time to participate in this study.

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Table 1. Baseline Characteristics of Patients According to Opioid Use at Baseline.

	Using Opioids at Baseline (n = 116)	**Not Using Opioids at Baseline (n = 913)**	***p* value***
Mean age in years at baseline (SD)	57.4 (15.5)	52.0 (17.0)	0.001
Female sex (%)	63 (54.3)	500 (54.8)	0.93
Married or co-habiting (%)	80 (69.6)	631 (69.6)	0.99
University graduate/professional (%)	29 (25.4)	358 (39.6)	0.003
Tobacco user (%)	9 (7.8)	58 (6.4)	0.57
Alcohol user (%)	79 (69.3)	668 (73.8)	0.31
IBD type (%)			
CD	66 (58.9)	393 (43.3)	
UC	40 (35.7)	453 (49.9)	
IBD-U	6 (5.4)	61 (6.7)	0.007
CD location (%)			
Ileal	25/66 (37.9)	134/392 (34.2)	
Colonic	13/66 (19.7)	121/392 (30.9)	
Ileocolonic	28/66 (42.4)	137/392 (34.9)	0.17
Stricturing CD (%)	18/66 (27.3)	112/393 (28.5)	0.84
Penetrating CD (%)	12/66 (18.2)	51/393 (13.0)	0.26
Perianal CD (%)	8/66 (12.1)	59/393 (15.0)	0.54
Previous intestinal resection (%)	38 (33.9)	132 (14.5)	<0.001
UC extent (%)			
Proctitis	11/40 (27.5)	139/447 (31.1)	
Left-sided	13/40 (32.5)	170/447 (38.0)	
Extensive	16/40 (40.0)	138/447 (30.9)	0.49
Current 5-aminosalicylate use (%)	49 (43.8)	499 (55.0)	0.024
Current immunomodulator use (%)	34 (30.4)	252 (27.8)	0.57
Current biologic use (%)	29 (25.9)	191 (21.1)	0.53

Current glucocorticosteroid use (%)	8 (7.1)	25 (2.8)	0.013
Current antidepressant use (%)	44 (37.9)	126 (13.8)	<0.001
Diagnosed with IBD in the last 12 months (%)	9 (7.8)	64 (7.1)	0.78
Self-reported current flare at baseline (%)	39 (33.9)	151 (16.6)	<0.001
Active disease on HBI or SCCAI at baseline (%)	69 (61.1)	304 (33.8)	<0.001
HADS-anxiety categories at baseline (%)			
Normal	48 (42.1)	525 (59.0)	
Borderline abnormal	30 (26.3)	186 (20.9)	
Abnormal	36 (31.6)	179 (20.1)	0.002
HADS-depression categories at baseline (%)			
Normal	62 (53.9)	701 (78.1)	
Borderline abnormal	24 (20.9)	124 (13.8)	
Abnormal	29 (25.2)	73 (8.1)	<0.001
PHQ-12 somatoform symptom-reporting categories at baseline (%)			
Minimal	8 (7.9)	263 (31.3)	
Low	23 (22.8)	321 (38.2)	
Medium	46 (45.5)	188 (22.5)	
High	24 (23.8)	68 (8.1)	<0.001
Rome IV IBS-type symptoms at baseline (%)	30 (29.7)	135 (15.5)	0.001
Mean SIBDQ score at baseline (SD)	42.2 (14.4)	51.8 (12.4)	<0.001

*Independent samples *t*-test for comparison of normally distributed continuous data and χ^2 for comparison of categorical data between groups.

Table 2. Clinical Outcomes of Patients According to Opioid Use at Baseline Over 12-month Longitudinal Follow-up.

	Using Opioids at Baseline (n = 116)	**Not Using Opioids at Baseline (n = 913)**	***p* value***	**Unadjusted HR (95% CI)**	***p* value**	**Adjusted HR (95% CI)**	***p* value**
Flare of disease activity (%)	15 (12.9)	139 (15.2)	0.51	0.87 (0.51 – 1.49)	0.61	0.67 (0.34 – 1.35)	0.26
Glucocorticosteroid prescription due to uncontrolled IBD activity (%)	5 (4.3)	66 (7.2)	0.24	0.60 (0.24 – 1.49)	0.27	0.48 (0.16 – 1.44)	0.19
Escalation of IBD therapy due to uncontrolled IBD activity (%)	13 (11.2)	117 (12.8)	0.62	0.90 (0.51 – 1.59)	0.71	0.85 (0.42 – 1.71)	0.64
Hospitalization due to uncontrolled IBD activity (%)	9 (7.8)	31 (3.4)	0.022	2.40 (1.14 – 5.03)	0.021	2.15 (0.81 -5.74)	0.13
Intestinal resection due to uncontrolled IBD activity (%)	6 (5.2)	11 (1.2)	0.002	4.44 (1.64 – 12.0)	0.003	7.09 (1.63 – 30.9)	0.009
Any of the above (%)	24 (20.7)	165 (18.1)	0.49	1.19 (0.78 – 1.83)	0.42	0.97 (0.56 – 1.69)	0.91

*χ^2 for comparison of data between groups.

Table 3. Clinical Outcomes of Patients According to Opioid Use at Baseline, Other Than Codeine or Dihydrocodeine, Over 12-month Longitudinal Follow-up.

	Using Opioids at Baseline (n = 39)	**Not Using Opioids at Baseline (n = 913)**	***p* value***	**Unadjusted HR (95% CI)**	***p* value**	**Adjusted HR (95% CI)**	***p* value**
Flare of disease activity (%)	6 (15.4)	139 (15.2)	0.98	1.08 (0.48 – 2.45)	0.85	0.83 (0.27 – 2.58)	0.74
Glucocorticosteroid prescription due to uncontrolled IBD activity (%)	1 (2.6)	66 (7.2)	0.27	0.36 (0.05 – 2.61)	0.31	0.32 (0.04 – 2.86)	0.31
Escalation of IBD therapy due to uncontrolled IBD activity (%)	3 (7.7)	117 (12.8)	0.35	0.61 (0.19 – 1.91)	0.39	0.51 (0.11 – 2.31)	0.38
Hospitalization due to uncontrolled IBD activity (%)	4 (10.3)	31 (3.4)	0.026	3.23 (1.14 – 9.15)	0.027	5.08 (1.12 – 23.0)	0.035
Intestinal resection due to uncontrolled IBD activity (%)	3 (7.7)	11 (1.2)	0.001	6.75 (1.88 – 24.2)	0.003	42.9 (3.36 – 548)	0.004
Any of the above (%)	8 (20.5)	165 (18.1)	0.70	1.21 (0.60 – 2.47)	0.60	0.96 (0.35 – 2.66)	0.94

*χ^2 for comparison of data between groups.

Figure 1. Survival Analysis for Occurrence of Intestinal Resection According to Opioid Use at Baseline.