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The Relationship Between Opioid Use and Healthcare Utilization in Patients With Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis

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Background: Pain is commonly experienced by patients with inflammatory bowel disease (IBD). Unfortunately, pain management is a challenge in IBD care, as currently available analgesics are associated with adverse events. Our understanding of the impact of opioid use on healthcare utilization among IBD patients remains limited.

Methods: A systematic search was completed using PubMed, Embase, the Cochrane Library, and Scopus through May of 2020. The exposure of interest was any opioid medication prescribed by a healthcare provider. Outcomes included readmissions rate, hospitalization, hospital length of stay, healthcare costs, emergency department visits, outpatient visits, IBD-related surgeries, and IBD-related medication utilization. Meta-analysis was conducted on study outcomes reported in at least 4 studies using random-effects models to estimate pooled relative risk (RR) and 95% confidence interval (CI).

Results: We identified 1969 articles, of which 30 met inclusion criteria. Meta-analysis showed an association between opioid use and longer length of stay (mean difference, 2.25 days; 95% CI, 1.29-3.22), higher likelihood of prior IBD-related surgery (RR, 1.72; 95% CI, 1.32-2.25), and higher rates of biologic use (RR, 1.38; 95% CI, 1.13-1.68) but no difference in 30-day readmissions (RR, 1.17; 95% CI, 0.86-1.61), immunomodulator use (RR, 1.13; 95% CI, 0.89-1.44), or corticosteroid use (RR, 1.36; 95% CI, 0.88-2.10) in patients with IBD. On systematic review, opioid use was associated with increased hospitalizations, healthcare costs, emergency department visits, outpatient visits, and polypharmacy.

Discussion: Opioids use among patients with IBD is associated with increased healthcare utilization. Nonopioid alternatives are needed to reduce burden on the healthcare system and improve patient outcomes.

Lay Summary

Pain control in inflammatory bowel disease presents a challenge due to the potential for adverse effects of opioids in this population. This systematic review and meta-analysis demonstrates that opioid use in inflammatory bowel disease is associated with increased healthcare utilization.

Key Words: Inflammatory Bowel Disease, Ulcerative Colitis, Crohn's Disease, Opioids, Healthcare utilization

Introduction

Approximately 1.4 million Americans suffer from inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC).[1] While the clinical presentation of IBD varies by disease extent and location, abdominal pain is common symptom in both patients with CD and UC.[2] However, pain management presents a challenge in IBD, as available analgesics have significant potential for adverse events in this population. For example, analysis of a prospective cohort of over 6000 patients with CD in the TREAT (Therapy, Resource, Evaluation, and Assessment Tool) registry demonstrated increased mortality in patients taking chronic opioids.[3] A similar mortality risk has also been identified in both patients with UC and CD who are prescribed high doses of opioids.[4,5] Opioid use in patients with IBD has also been linked to increased risk of serious infection and opioid use disorder.[3,6,7] Despite the negative safety profile, it is estimated that 21% of outpatients and 62% of inpatients

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with IBD are prescribed opioids at some point in their disease course.[8]

The cost of IBD care is primarily driven by hospitalizations, emergency department (ED) visits, surgeries, and pharmaceuticals.[9] As the cost of managing IBD continues to rise, it is vital that we identify potential risk factors for high expenditure in the IBD population.[10] Recent literature has established opioid use, along with psychiatric disorders, anemia, biologic use, corticosteroid use, and disease severity, as a risk factor for increased healthcare spending in patients with IBD.[11–13] While opioid use may predict increased spending, it remains unclear which aspects of healthcare utilization are driving costs in patients with IBD who use opioids. Several studies have attempted to draw connections between opioid use and readmission rates, hospitalizations, length of stay (LOS), and IBD-related surgeries; however, results have been mixed. Furthermore, there is significantly variability in patient characteristics and in the definition of opioid use. Given the degree of variability between studies, a pooled analysis is needed to better understand this relationship between healthcare utilization and opioid use in patients with IBD. Therefore, we performed a systematic review and meta-analysis to determine if opioid use is associated with increased healthcare utilization among patients with IBD.

Methods

Study Eligibility

The aim of this study was to determine if prescription opioid use is a risk factor for high healthcare utilization in the IBD population. Studies that reported healthcare utilization outcomes in patients with IBD using opioids were eligible for inclusion. For the purposes of this review, any study documenting an opioid prescribed by a medical provider during the study period was included. This included opioids prescribed in the outpatient setting and during a single inpatient admission. Studies examining opioid use disorder were excluded from the main analysis; however, they were incorporated into the sensitivity analysis. The decision to exclude studies using opioid use disorder as a surrogate for opioid use was due to the fact that opioid use disorder does not necessarily represent active opioid or prescription opioid use. Randomized controlled trials, prospective and retrospective cohort studies, longitudinal, and case-control studies were eligible for inclusion. Case series and case reports were excluded due to low-quality methodology, as were conference abstracts due to incomplete data reporting.

Search Strategy

A systematic search of opioid use in IBD was performed by an experienced health sciences librarian (C.S.) using MEDLINE (PubMed), EMBASE, the Cochrane Library, and Scopus. No filters were used in the initial search to reduce the risk of bias. The initial search and included studies in any language, publication year, or journal. Both published and nonpublished (conference abstracts, oral presentations) were also included in the initial search. Findings were reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement, elaboration, and explanation and the Statement for Reporting Literature Searches for Systematic Reviews.[14–16] All searches were completed by May 2020.

Outcomes

Healthcare utilization is defined as the "quantification or description of the individual use of health services for the purposes of disease prevention or cure," and it is typically measured by the number of services in a given period of time divided by the population or as a total aggregate number.[17] For the purposes of this study, we focused our primary outcomes on 30-day readmission rates, hospitalizations, LOS, total healthcare costs, ED visits, outpatient visits, polypharmacy, and use of private or public insurance. Secondary outcomes included IBD-related surgeries and medications as potential markers for disease severity. Surgeries included both a prior history of IBD-related surgery and surgeries that occurred during the study period. Medications included biologics (infliximab, adalimumab, certolizumab pegol, golimumab, vedolizumab, and ustekinumab), immunomodulators (azathioprine, 6-mercaptapurine, and methotrexate), steroids (prednisone, methylprednisolone, or budesonide), and small molecules (tofacitinib). Meta-analysis was conducted on outcomes that were reported in at least 4 studies. Studies were included in the systematic review if they were not eligible for inclusion in the meta-analysis but otherwise met the study inclusion criteria.

Study Selection and Data Extraction

Titles and abstracts were independently reviewed by J.L.S. and J.J. for study eligibility and data extraction. If study selection were discordant, the full text was reviewed, and consensus was reached via discussion between the 2 reviewers (J.L.S. and J.J.). A third reviewer, J.A.B., was available for adjudication if no consensus on inclusion could be reached.

Data extraction was independently performed by J.L.S., J.J., and L.G.-H. Study demographics, including author, year of publication, country of publication, study design, sample size, age range, IBD subtype, and definition of opioid use were extracted independently by JLS and L.G.-H. For discordant data, a consensus was reached by discussion between the 2 reviewers (J.L.S. and L.G.-H.). The remaining data were extracted by J.L.S. and J.J. using a customizable data extraction tool created in DistillerSR Literature Review Software version 2.34.1 (Evidence Partners, Ottawa, ON, Canada). For studies eligible for meta-analysis, the data extraction tool contained 2 × 2 tables used to collect raw data calculated from odds ratios (ORs) and relative risks (RRs). The data collection tool was also used to collect descriptions of the statistical findings for each of the systematic review outcomes (hospitalizations, ED visits, costs, insurance type, and polypharmacy). Discrepant data were re-evaluated by J.L.S. and J.J. and resolved via discussion between reviewers. Both E.M.B. and J.A.B. were available for adjudication if the discrepancy could not be resolved to consensus. We were unable to extract data from Anderson et al[19] and Tinsley et al.[29] The corresponding authors were contacted but the critical data were either unavailable or no response was received.

Risk of Bias Assessment and Sensitivity Analysis

A risk of bias assessment was independently performed by J.L.S. and E.M.B. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of all cohort and case-control studies included in the analysis (Table 1).[42] An NOS score of 7 or higher was used to identify studies with a low risk of bias.[43] As proposed by Egger et al[44] a visual inspection of

Table 1. Study characteristics.

First Author	Year	Country	Study Design	Sample Size	Mean Age (y)	Disease (%CD, %UC, %IC)	Inpatient vs Outpatient Opioid Use	Definition of Opioid Use	NOS
Alley[18]	2019	United States	Retrospective cohort	76 171	45.3	52% CD, 48% UC	Outpatient	Extended opioid use defined as 60-d supply or more of opioids in a single year	7
Anderson[19]	2018	United States	Prospective cohort	447	39.4	65% CD, 33% UC, 2% IC	Outpatient	1 or more prescriptions during 2-y study period	7
Berry[20]	2020	United States	Retrospective cohort	57	32	56% CD, 40% UC, 4% IC	Inpatient	Any opioid use during hospitalization, excluding those for procedural sedation	7
Buckley[21]	2013	United States	Cross-sectional	104 582	—	46% CD, 53% UC, 1% IC	Outpatient	Any outpatient opioid dispensed during the study period	NA
Burr[4]	2018	United Kingdom	Retrospective cohort	8866	—	40% CD, 60% UC	Outpatient	Any opioid prescribed by primary care during study period	7
Cheung[22]	2015	United States	Cross-sectional	108	50.5	100% CD	Outpatient	Any opioid within the month prior to hospital admission	NA
Chitnavis[23]	2019	United States	Retrospective cohort	497	52.9	100% UC	Outpatient	3 consecutive prescriptions for opioids filled or 2 filled in a 6-mo period	6
Christian[24]	2017	United States	Retrospective cohort	498	39.4	67% CD, 31% UC, 2% ID	Outpatient	Opioid prescription at discharge	7
Click[13]	2016	United States	Prospective cohort	338	—	54% CD, 42% UC, 4% IC	Outpatient	Any outpatient opioid prescription during the study period	6
Coates[25]	2020	United States	Retrospective cohort	542	40.4	100% CD	Outpatient	Opioid prescription provided prior to index visit	6
Cross[26]	2005	United States	Retrospective cohort	291	40.2	100% CD	Outpatient	Any opioid used for purpose of analgesia, excluding 2-mo period following surgery	5
Dalal[27]	2020	United States	Retrospective cohort	862	40.4	66% CD, 34% UC	Inpatient	IV and non-IV opioids prescribed during hospital admission	8
Hanson[28]	2009	United States	Case-control	200	44.9	78% CD, 22% UC	Outpatient	Opioid prescription taken for IBD-related pain at initial clinic visit	7
Hazratjee[29]	2013	United States	Retrospective cohort	429	41.2	72% CD, 38% UC	Both	(1)Any opioids prescribed during admission (2)Opioids prescribed at discharge	8
Kelso[30]	2017	United States	Retrospective Cohort	113	48.5	48% CD, 52% UC	Inpatient	IV opioid during admission	7
Li[31]	2016	United States	Retrospective cohort	1331	41.1	100% CD	Both	Any inpatient or outpatient opioid prescription 1 mo prior to surgery	5
Lian[32]	2010	United States	Retrospective cohort	223	38.7	100% UC	Inpatient	Oral or IV opioids given while inpatient (excluding after colectomy)	6

Table 1. Continued

First Author	Year	Country	Study Design	Sample Size	Mean Age (y)	Disease (%CD, %UC, %IC)	Inpatient vs Outpatient Opioid Use	Definition of Opioid Use	NOS
Lichtenstein[3]	2012	United States, Canada	Prospective cohort	6273	42.5	100% CD	Both	Any opioid use from enrollment to 6-mo data collection period	5
Limsrivilai[11]	2017	United States	Retrospective cohort	1430	40.0	60% CD, 40% UC	Both	Any opioid prescription use during the study period	7
Long[33]	2012	United States	Retrospective cohort	117	31.9	72% CD, 28% UC	Inpatient	Any opioids prescribed during hospital admission, excluding those used for sedation or postoperatively	6
Mudireddy[34]	2017	United States	Retrospective cohort	439	38	67% CD, 33% UC	Both	(1)Opioids on admission (2)Opioids on discharge	8
Nugent[35]	2016	Canada	Case-control	3694	50	—	Outpatient	At least 1 opioid prescription in the previous year	8
O'Brien[36]	2020	United States	Retrospective cohort	118	—	100% CD	Both	Any opioid use 6 mo prior to surgery	6
Parian[37]	2015	United States	Retrospective cohort	190	70.2[a]	50% CD, 50% UC	Outpatient	Opioids listed on outpatient medication list during clinic visit	5
Park[9]	2020	United States	Case-control	52 782	48.3	45% CD, 55% UC	Outpatient	Claims data with at least 1 opioid prescription	7
Pauly[38]	2017	United States	Retrospective cohort	47 164	41.8	100% CD	Outpatient	90-d supply of opioids in a 6-mo period without any 30-d gaps between prescriptions	6
Sanford[39]	2014	Canada	Cross-sectional	100	41.3	100% CD	Outpatient	Use at least 1 opioid drug weekly for control of Crohn's pain	NA
Targownik[5]	2014	Canada	Cross-sectional	4217	—	47% CD, 53% UC	Outpatient	Heavy opioid use defined as 50 MME/d for 30 d in any 1-y period AND at least 2 prescriptions in the same 1-y period	NA
Tinsley[40]	2015	United States	Retrospective cohort	229	37.28	100% UC	Outpatient	Opioids prescribed at discharge	7
Wren[41]	2018	United States	Retrospective cohort	93 668	23.1[b]	52% CD, 40% UC, 8% IC	Outpatient	Chronic opioid use defined as 2 or more opioid prescriptions in a year; persistent chronic opioid use defined as 4 or more years of use	6

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; IC, indeterminate colitis; IV, intravenous; NA, not applicable; NOS, Newcastle-Ottawa Scale; UC, ulcerative colitis.
[a]Included only patients 65 years of age and older.
[b]Included only patients 15-29 years of age.

funnel plots for asymmetry was used to assess publication bias. Floor and ceiling effects were identified in funnel plots when relevant (Supplemental Figure 1).

A post hoc, sensitivity analysis was performed to assess the stability of our meta-analysis findings by using an alternative definition of opioid use, which included opioid use disorder. We were able to compare the RRs between our main and alternative definitions of opioid use to determine the influence of the individual dataset on the pooled analysis.

Statistical Analysis

Pooled rates and 95% confidence intervals (CIs) were calculated from the eligible studies using random-effects meta-analysis according to the methods described by Hartung-Knapp-Sidik-Jonkman.[45] A random-effects model was used due to the heterogeneity in study setting, study population, and study design. The proportions and their 95% CIs were presented as forest plots. Statistical heterogeneity was assessed using the I^2 statistic in which ≥30% signifies significant heterogeneity. We performed several subgroup analyses based on the setting and the timing of opioid administration. All analyses were performed using R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study Selection

A total of 2059 studies were identified using our search strategy (Figure 1). Ninety studies were removed due to duplication, leaving 1969 unique citations. The titles and abstracts of these studies were screened, and 1882 were removed based on relevance. A total of 87 studies were fully reviewed, and an additional 57 were removed for the following reasons: lack of healthcare utilization outcome (n = 19), abstract only (n = 18), duplicate (n = 9), opioid use disorder or dependence (n = 5), not relevant to opioid use (n = 2), pediatric populations only (n = 2), review article (n = 1), or editorial (n = 1). A total of 30 unique studies were included in the final meta-analysis and systematic review.

Study Characteristics

The 30 included citations comprised 20 retrospective cohorts, 3 prospective cohorts, 4 cross-sectional studies, and 3 case-control studies (Table 1). The average age of the study participants was 38 years. All studies included patients 18 years of age and older, except for Wren et al,[41] who studied patients 15 to 29 years of age. Most studies included both patients with CD and UC (n = 19), with 8 studies including only patients with CD and 3 studies including only patients with UC. Most studies were conducted in the United States (n = 26), but 3 studies from Canada and 1 from the United Kingdom were included.

30-Day Readmissions and Hospitalizations

Seven studies including a combined 4688 patients evaluated 30-day readmission rates in patients with IBD receiving opioids.[20,24,27,29,31,34,36] Pooled RR demonstrated no difference in readmission rates between patients with IBD who received opioids compared with those who did not (RR, 1.17; 95% CI, 0.86-1.61; I^2 = 43%) (Supplemental Figure 2).

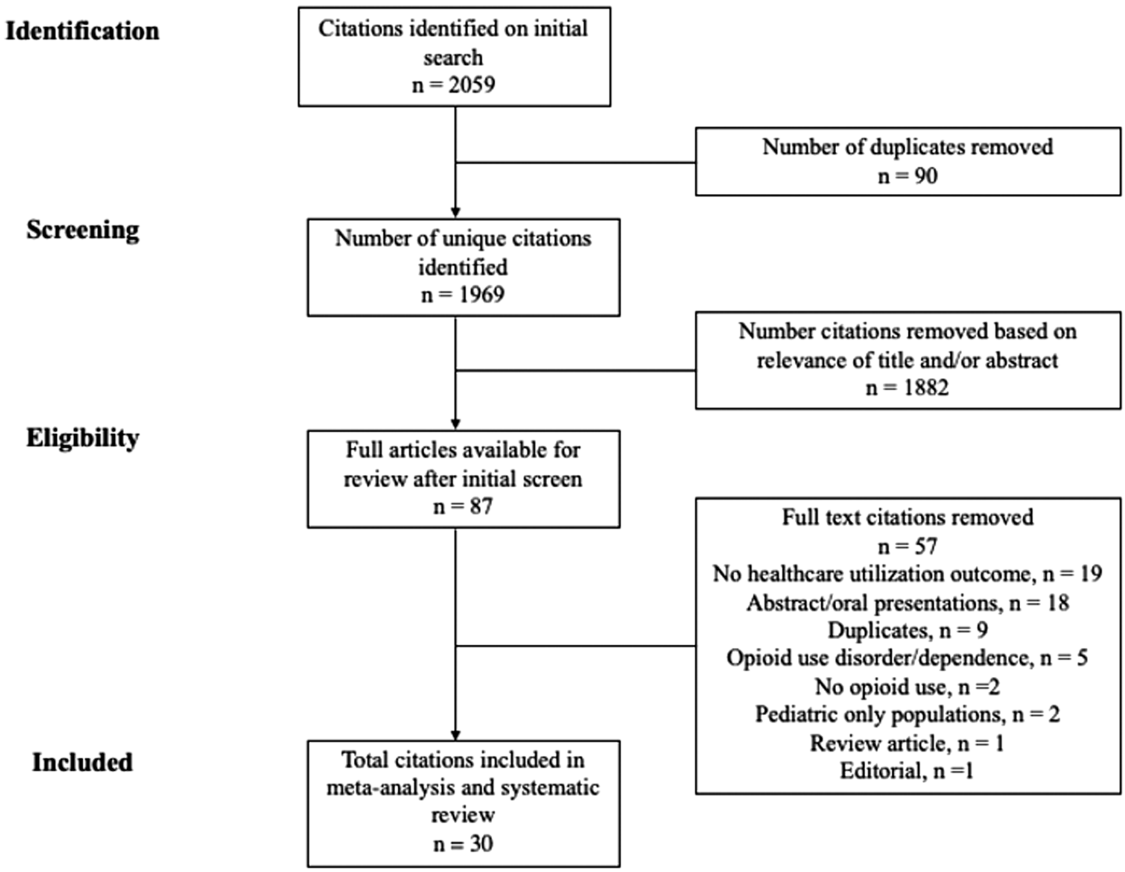

Figure 1. Search strategy flow diagram.

Additionally, subgroup analysis demonstrated no difference in readmission rates in those who received opioids prior to admission (RR, 1.81; 95% CI, 0.56-5.8; I^2 = 0%), during the admission (RR, 1.03; 95% CI, 0.75-1.43; I^2 = 10%), or at discharge (RR, 1.29; 95% CI, 0.97-1.71; I^2 = 0%) (Supplemental Figure 3). Similarly, Tinsley et al[40] demonstrated no difference in 30-day readmission rates between those who received opioids at discharge and those who did not (OR, 1.82; 95% CI, 0.48-6.93), but this study was not eligible for inclusion in the meta-analysis.

When examining hospitalization rate, 7 studies found a statistically significant association between opioid use and frequency of hospitalizations.[9,11,21,35,38,39,41] In contrast, Targownik et al[5] showed no difference in the hospitalization rate between heavy opioid users and those not taking opioids.

Length of Stay

Four studies including 2597 patients examined the relationship between hospital LOS and opioid use in patients with IBD.[27,31,32,36] Pooled mean differences (MDs) demonstrated that IBD patients who received opioids during the hospitalization had a higher LOS compared with those who did not (MD, 2.25 days; 95% CI, 1.29-3.22 days; I^2 = 61%) (Figure 2). One additional study by Kelso et al[30] showed that patients with an LOS >4 days were more likely to have received intravenous opioids compared with those with a shorter LOS. In contrast, Berry et al[20] demonstrated no difference in the LOS in patients who were prescribed opioids compared with those who were not.

Healthcare Costs

Five studies demonstrated an association between opioid use in patients with IBD and increased healthcare spending.[9,11,13,18,41] Two studies demonstrated that opioid users were more likely to be in the top quartile of spending, while Click et al[12] showed that opioid users were more likely to be in the top 5% of spenders.[11,13,18] Wren et al[41] demonstrated that 28.8% of patients prescribed opioids for 4 or more years spent >50 000 healthcare dollars a year compared with 9.2% of nonusers (P < .001).

ED and Outpatient Visits

Six studies examined the relationship between ED visits and opioid use in patients with IBD.[9,11,18,35,38,41] Five of these studies demonstrated that patients taking opioids had a greater number of ED visits compared with those not using opioids.[9,11,18,35,38] Wren et al[41] demonstrated that opioid users were more likely to have at least 1 ED visit in a given year.

The data examining the relationship between outpatient visits and opioid use in patients with IBD was limited to 2 studies.[21,41] Wren et al[41] showed that patients with chronic opioid use had a greater number of outpatient visits during the study period. This result was more pronounced in those who had been using chronic opioids for 4 or more years. Similarly, Buckley et al[21] demonstrated that patients with IBD using opioids had a greater frequency of outpatient visits compared with those not using opioids.

Polypharmacy

Four studies examined the relationship between polypharmacy and opioid use in IBD patients.[21,26,37,41] Three studies demonstrated a statistically significant association between opioid use and polypharmacy in IBD patients,[21,26,41] while Parian et al[37] found no significant difference between opioid users and nonusers on mild, moderate, or severe polypharmacy.

Insurance Coverage

Three studies examined the relationship between opioid use in patients with IBD and use of public vs private health insurance.[21,23,33] Chitnavis et al[23] failed to show a significant difference in opioid use among patients using disability insurance or Medicaid insurance compared with those with commercial insurance (OR, 1.77; 95% CI, 0.49-6.38). Similarly, Long et al[33] showed no difference in opioid prescriptions between those with and without insurance. In contrast, Buckley et al[21] showed that 48% of patients with IBD with commercial insurance or Medicare were prescribed at least 1 opioid, compared with 73% of those with Medicaid.

IBD-Related Surgeries

Seven studies including 2278 patients examined the relationship between a prior history of gastrointestinal surgery and opioid use in patients with IBD.[19,22,25,27,28,33,36] Pooled RR demonstrated that patients with a history of prior IBD-related surgery were more likely to be prescribed opioid medications (RR, 1.72; 95% CI, 1.32-2.25; I^2 = 69%) (Figure 3). On subgroup analysis, patients with a history of IBD-related surgery were more likely to have received outpatient opioid prescriptions (RR, 1.53; 95% CI, 1.17-1.99; I^2 = 24%) but

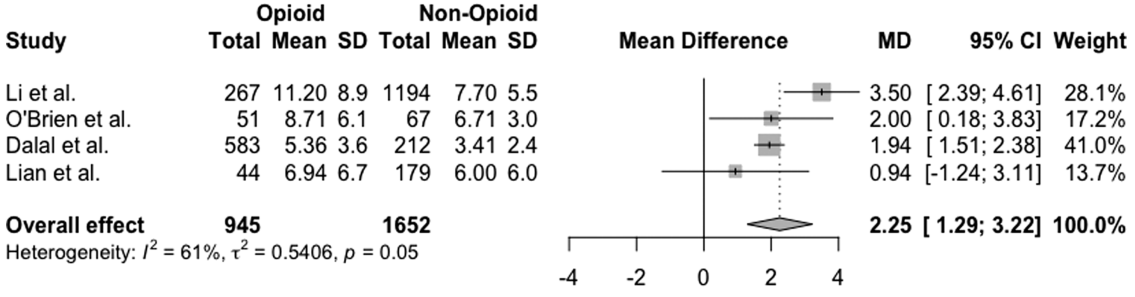

Figure 2. Association between hospital length of stay and opioid use among patients with inflammatory bowel disease. CI, confidence interval; MD, mean difference.

not inpatient opioid prescriptions (RR, 2.39; 95% CI, 0.24-23.36; I^2 = 30%) (Supplemental Figure 3).

An additional 8 studies including 90 665 patients examined the relationship between gastrointestinal surgery during the study period and opioid use in patients with IBD.[4,5,21,25,27,32,33,41] Pooled RR demonstrated that patients who underwent IBD-related surgery during the study period were more likely to be taking opioid medications (RR, 1.65; 95% CI, 1.09-2.49; I^2 = 99%) (Figure 4). However, the results no longer reached statistical significance (with a much smaller sample size) when separated by outpatient opioid use (RR, 1.83; 95% CI, 0.95-3.53; I^2 = 99%) and inpatient opioid use (RR, 1.37; 95% CI, 0.49-3.87; I^2 = 69%) (Supplemental Figure 3).

Medications

Biologics

Nine studies including 108 662 patients examined the relationship between biologic use (infliximab, adalimumab, certolizumab pegol, golimumab, vedolizumab, and ustekinumab) and opioid use in patients with IBD.[3,5,21,25,27,32,36,39,41] Pooled RR demonstrated that patients receiving biologic therapy were more likely to be taking opioid medications (RR, 1.38; 95% CI, 1.13-1.68; I^2 = 67%) (Figure 5).

Immunomodulators

Seven studies including 104 994 patients examined the relationship between immunomodulator use (azathioprine, 6-mercaptapurine, and methotrexate) and opioid use in patients with IBD.[4,5,21,25,27,39,41] Pooled RR demonstrated that patients receiving immunomodulator therapy were not more likely to be taking opioid medications (RR, 1.13; 95% CI, 0.89-1.44; I^2 = 84%).

Steroids

Seven studies including 102 961 patients examined the relationship between steroid use and opioid use in patients with IBD.[5,21,25,27,36,39,41] Pooled RR demonstrated that patients receiving steroid therapy were not more likely to be taking opioid medications (RR, 1.36; 95% CI, 0.88-2.10; I^2 = 96%).

Small molecules

No studies examining the relationship between opioids and tofacitinib were identified.

Risk-of-Bias Assessment and Sensitivity Analysis

Twelve of the 30 included studies scored <7 on the NOS, indicating greater risk for bias and potentially lower-quality

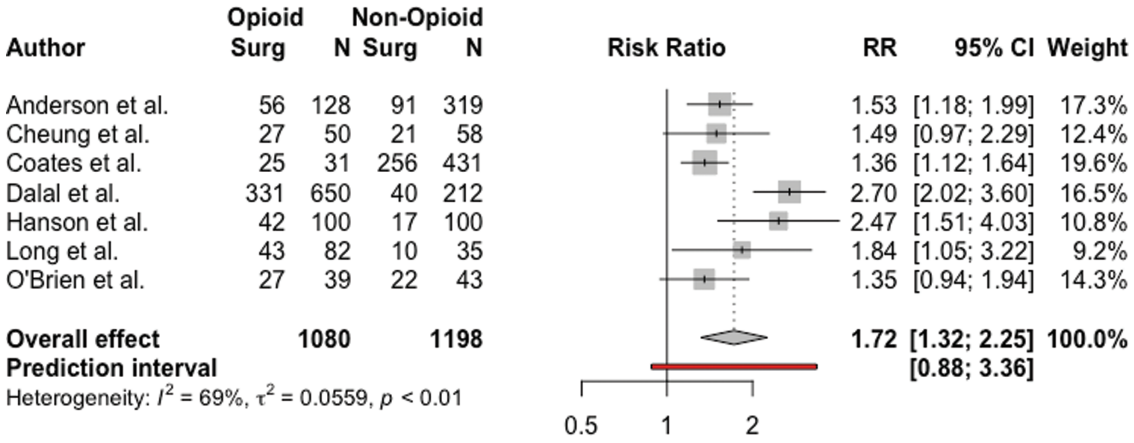

Figure 3. Association between prior inflammatory bowel disease–related surgery and opioid use among patients with inflammatory bowel disease. CI, confidence interval; RR, relative risk.

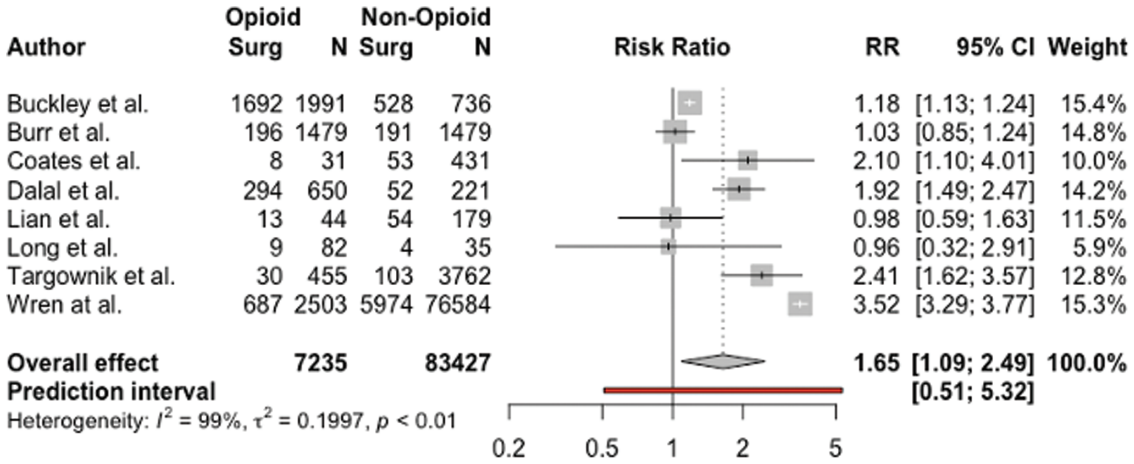

Figure 4. Association between inflammatory bowel disease–related surgery during the study period and opioid use among patients with inflammatory bowel disease. CI, confidence interval; RR, relative risk.

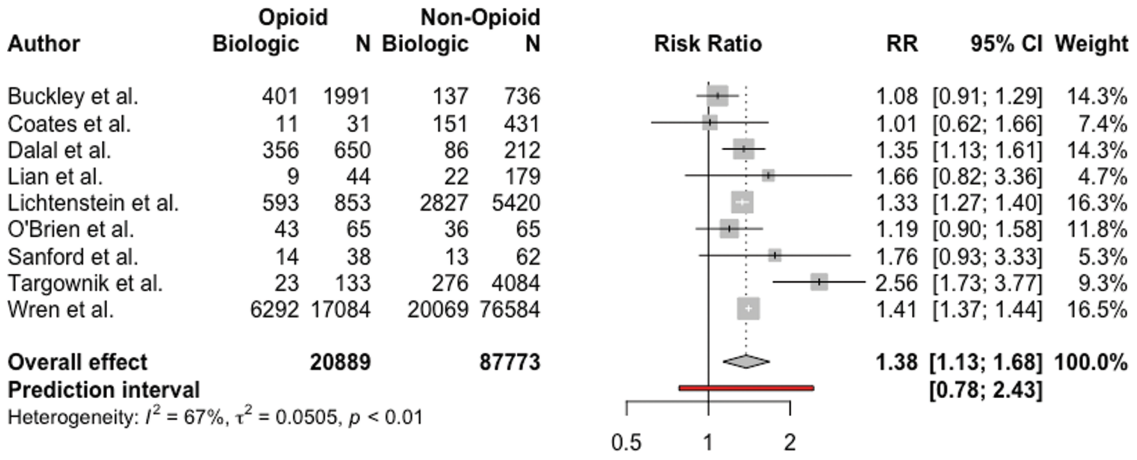

Figure 5. Association between biologic use and opioid use among patients with inflammatory bowel disease. CI, confidence interval; RR, relative risk.

studies.[42,43] Visual inspection of the funnel plots for each outcome study in the meta-analysis demonstrated relative symmetry, indicating low risk for publication bias.[44]

A post hoc, sensitivity analysis was performed using an alternative definition of opioid use, which included patients with opioid use disorders as well. This analysis added 487 729 patients from the Nationwide Readmissions Database.[46] Pooled RR continued to demonstrate a non–statically significant trend toward 30-day readmissions in patients with IBD who received opioids compared with those who did not (RR, 1.26; 95% CI, 0.94-1.67; I^2 = 78%) (Supplemental Figure 2). No additional utilization outcomes were available to perform additional analysis.

Discussion

To our knowledge, this is the first meta-analysis to demonstrate several important links between healthcare utilization and opioid use in patients with IBD. In this review, we identify that (1) there is a non–statistically significant trend toward increased 30-day readmission rates in patients with IBD who use opioids, regardless of whether opioids were given prior to admission, during the admission, or on discharge; (2) opioid use was associated with a longer inpatient LOS compared with patients with IBD who did not receive opioids; (3) prior IBD-related surgery is a risk factor for outpatient opioid use; and (4) inpatient opioid use did not increase risk for IBD-related surgery during admission. Similar to a recent meta-analysis, we found that biologics but not immunomodulators were associated with opioid use; however, unlike Niccum et al,[8] we did not find that use of corticosteroids was associated with increased opioid use.

On systematic review of the literature, we found that opioid use in patients with IBD was associated with increased hospitalizations, healthcare costs, ED visits, outpatient visits, and polypharmacy. The association between opioid use and increased outpatient visits can be expected due to the need for controlled substance monitoring and may not necessarily reflect a negative effect on utilization attributable to opioids themself. One could argue that increased outpatient visits could provide the opportunity for tight symptom monitoring, which may lead to improved patient outcomes as demonstrated in the CALM (Effect of Tight Control Management on Crohn's Disease) trial.[47] However, the increase in ED visits and hospitalizations indicates that patients using opioids are also more likely to interact with the healthcare system in the form of unplanned acute care.

With several studies indicating higher levels of healthcare utilization in patients prescribed opioids for musculoskeletal conditions,[48–51] it is perhaps not surprising that high utilization is also seen in patients with IBD who take opioids. What may be more intriguing is that we did not identify a statistically significant association between opioids and increased 30-day readmissions. Known risk factors for readmissions in patients with IBD include chronic pain, anxiety and depression, and medical complexity,[52,53] many of which are also listed as risk factors for opioid use.[54–56] The lack of association between opioid use and 30-day readmissions suggests that other factors such as mental health conditions and chronic pain may be driving the increased healthcare utilization independent of opioid use seen in patients with IBD. However, given that publicly available readmission databases typically do not include prescription claims data, the lack of direct association between opioid use and 30-day readmissions may simply be due to lack of available data. To test this hypothesis, we performed a sensitivity analysis to include studies using an alternative definition for opioid use, including patients with a diagnosis of substance use disorder, comparing the relationship between opioid use and 30-day readmissions. While this analysis added over 400 000 additional patients, the trend toward increased 30-day readmissions in patients using opioids remained nonsignificant. Furthermore, the addition of opioid use disorder to the analysis significantly increased the heterogeneity, indicating that studies using opioid use disorder as their exposure may be fundamentally different from studies looking at prescription opioid use. The findings from our sensitivity analysis suggests that the result and conclusions drawn from our study were not affected by the alternative definitions that could be made during the review process, and that results of our review can be regarded with a higher degree of certainty. The varying definitions among studies highlights the complexity involved in answering this question using retrospective and claims data, which often rely on surrogate markers of opioid use such as opioid use disorder or chronic pain and are prone to multiple confounding factors and biases.

A notable strength of this study was the subgroup analysis of inpatient vs outpatient opioid use. These data were

particularly helpful in determining the relationship between IBD-related surgery and the use of opioids in the acute inpatient phase vs the more chronic outpatient phase of care. Many clinicians avoid the use of opioids in an acute IBD exacerbation due to the concern that opioid-induced bowel dysfunction, a well-established entity in which gastrointestinal transit time is delayed due to binding of mu-receptor agonists in the enteric nervous system,[57,58] could lead to obstruction, ileus, or perforation. However, the results of our analysis showed no increased risk for surgery in patients who received opioids while admitted to the hospital. These results may indicate that a short course of opioids while admitted for an acute IBD flare may not be as dangerous as is generally regarded, though opioid use was associated with an increased LOS.

Interestingly, the subgroup analysis on outpatient opioid use did not show an association with increased IBD-related surgeries. However, only 2 of these studies, Targownik et al[5] and Wren et al,[41] specified the "heavy" and chronic use of opioids, respectively. Both of these studies demonstrated a strong association between opioid use and need for surgery. The remaining 3 studies defined opioid use more broadly, even including a single outpatient prescription. Therefore, while our subgroup analysis did not identify outpatient opioid use as a predictor of surgery, chronic, outpatient opioid use may still be a significant risk factor for future surgery.

Additionally, our subgroup analysis showed that prior IBD-related surgery was a risk factor for outpatient opioid prescriptions. With the ongoing opioid epidemic and increasing number of opioid-related deaths, it is vital that we identify individuals who are at risk for chronic opioid use, misuse, and addiction.[59] Patients with IBD are already at risk for developing chronic abdominal pain, particularly if they have severe disease or concomitant anxiety and depression.[60] Our analysis suggests that a history of prior IBD-related surgery as a potential risk factor for chronic pain and chronic opioid use, and clinicians should strongly consider nonopioid alternatives in patients with prior bowel surgery.

Our analysis had 2 main limitations. The first was the quality of studies included in our review. Currently there are no prospective, controlled trials dedicated to the study of the effects of opioid use in patients with IBD, and as result, the majority of included studies were retrospective cohorts, making it difficult to determine causality. Additionally, of the studies included, 40% scored <7 on the NOS (Table 1), indicating potential for bias related to study quality. Therefore, it remains unclear whether opioid use itself is driving higher rates of healthcare utilization or if high rates of healthcare utilization put patients with IBD at risk for exposure to opioids. Furthermore, some research suggests that covariates such as quality of life,[19,39] mental health conditions,[54–56] substance abuse or dependence,[46,56,61] and functional gastrointestinal disorders[55,62,63] could be driving the relationship between opioid use and healthcare utilization.

The second significant limitation is this the degree of heterogeneity. The I^2 value in this study ranged from 24% to 99%, which was consistent with the I^2values reported in the recently published meta-analysis by Niccum et al.[8] The high I^2 values seen in our analysis and Niccum et al suggest a large degree of variability between included studies and call into question the accuracy of these meta-analyses. However, it also highlights the need for more rigorous research studies focused on potential outcomes of opioid use in the IBD population. Much of the data were collected from patient characteristic tables of studies not specifically focused on opioid use, which likely accounts for the observed degree of variability between studies. Despite the I^2 values, our analysis and the analysis performed by Niccum et al are the only pooled data available on the topic of opioid use and IBD.

In summary, the results of this systematic review and meta-analysis indicate that opioid use in IBD patients is a risk factor for high healthcare utilization. However, it is unclear if opioid use is the cause of this increased utilization or is merely an indicator of more severe disease. Regardless, with the ongoing opioid epidemic and rising healthcare costs, clinicians should continue to make all efforts to reduce opioid use in this population. There remains a critical need to identify nonopioid alternatives for pain in patients with IBD.

Supplementary Data

Supplementary data is available at *Inflammatory Bowel Diseases* online.

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Conflicts of Interest

P.D.R.H. has received consulting fees from AbbVie and Pfizer. J.A.B. has received consulting fees from Buhlmann Diagnostics Corp. All other authors report no relevant disclosures.

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