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Short-Term and Long-Term Opioid Use Is Associated With Poor Outcomes in Outpatients With Inflammatory Bowel Disease

L. TELFER[1], **S. DALESSIO**[2], **A. TINSLEY**[2], **M. COATES**[2]

[1]Penn State College of Medicine, Hershey, Pennsylvania

[2]Division of Gastroenterology & Hepatology, Penn State College of Medicine, Hershey, Pennsylvania

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is characterized by chronic inflammation of the gastrointestinal tract. IBD patients typically experience many problematic symptoms, including abdominal pain.[1] Abdominal pain in IBD is one of the primary drivers of patient decision-making and healthcare resource utilization.[2] Managing the underlying inflammation often helps, but some patients continue to experience pain. Finding safe and effective analgesic therapies in this setting has proven to be very challenging.

Opioids are frequently prescribed to treat pain associated with IBD. Unfortunately, they are associated with many problems in IBD, including increased risk of emergency room visits, hospitalization, surgery, and mortality.[3,4] Chronic opioid use may also exacerbate symptoms and induce IBD flares, prompting discontinuation, thus increasing the risk of opioid withdrawal syndrome.[5] Ironically, there is no published evidence that opioids even help to improve abdominal pain in IBD, particularly in the long term. Notably, most studies investigating opioid use in IBD have been limited to hospitalized patients, and few have directly evaluated the impact of opioid prescription length.

We performed a retrospective, population-based cohort study using the TriNetX Diamond Network to (a) compare the impact of opioid use on health-associated outcomes in IBD outpatients and (b) evaluate for a differential impact on these outcomes based upon the length of opioid prescription. Please refer to the Supplemental Methods for details about data abstraction and analysis.

Correspondence: Address correspondence to: Matthew Coates, MD, PhD, Division of Gastroenterology and Hepatology, Penn State University Hershey Medical Center, 500 University Drive, Hershey, Pennsylvania 17033. mcoates@pennstatehealth.psu.edu.

Conflicts of Interest:
The authors disclose no conflicts.

Ethical Statement:
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Reporting Guidelines:
Helsinki Declaration.

Supplementary Materials
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In the comparison of short-term opioid users (opioid-use disorder and/or opioid use of 6 weeks or less) and nonusers (no record of opioid-use disorder or use), after propensity score matching, each cohort had 40,359 patients that were included in the analysis. Short-term opioid users were more likely to use corticosteroids (relative risk [RR]: 2.517, 95% confidence interval [CI]: 2.438–2.597, $P < .001$) and to utilize emergency department (ED) services (RR: 1.315, 95% CI: 1.271–1.361, $P < .001$). There were no statistically significant differences between cohorts in the risk of mortality (RR: 0.822, 95% CI: 0.6721–1.006, $P = .057$) and IBD-related surgery (RR: 0.75, 95% CI: 0.407–1.382, $P = .354$) (Figure A).

In the comparison of long-term opioid users (opioid-use disorder and/or opioid use of greater than 6 weeks) and nonusers, after propensity score matching, each cohort had 1380 patients that were included in the analysis. Long-term opioid users were more likely to use corticosteroids (RR: 2.383, 95% CI: 1.998–2.842, $P < .001$) and to utilize ED services (RR: 2.083, 95% CI: 1.813–2.394, $P < .001$) than the non-opioid user cohort. The cohorts did not show a statistically significant difference in the risk of death (RR: 1.1, 95% CI: 0.469–2.582, $P = .827$) or IBD-related surgery (RR: 1, 95% CI: 0.418–2.395, $P = 1.0$) (Figure B).

In the comparison of short-term opioid users and long-term opioid users, after propensity score matching, each cohort had 1385 patients that were included in the analysis. Long-term opioid users were more likely to utilize ED services (RR: 1.572, 95% CI: 1.39–1.778, $P < .001$) than short-term users. The cohorts did not show a statistically significant difference in the risk of death (RR: 1.1, 95% CI: 0.469–2.582, $P = .8266$), IBD-related surgery (risk ratio: 1, 95% CI: 0.418–2.395, $P = 1.0$), or corticosteroid use (RR: 0.897, 95% CI: 0.794–1.013, $P = .0802$) (Figure C).

We demonstrated that opioid use, independent of duration, is associated with increased risk of ED visits and corticosteroid use in an outpatient IBD cohort. We also found a potential “dose-related” effect of prescription opioid use, as long-term users demonstrated an increased risk of ED visits when compared to short-term users. Opioid use demonstrated no significant impact on the risk of IBD-related surgery or death.

There were similarities to earlier investigations of opioid use in IBD. For example, a previous large-scale retrospective cohort study of IBD patients reported that prolonged opioid use (≤60 days) is associated with increased risk of urgent care and ED visits.[6] A separate study demonstrated an increased risk of ED visits among opioid users with IBD.[7] Another cross-sectional study of Crohn’s disease patients found that opioid users were more likely to use corticosteroids.[8]

Unlike previous studies, we did not find an association between opioid use and IBD-related surgery or death. A recent meta-analysis demonstrated that there was a higher likelihood of prior IBD-related surgeries among opioid users[9] (though this association lost significance when prescriptions were divided by inpatient/outpatient status). Additionally, previous English[4] and Canadian studies associated heavy opioid use with mortality in IBD.[10] Notably, these associations utilized opioid dosage (eg, morphine equivalent or number of prescriptions), rather than length of opioid prescription (as we did). We also focused on IBD outpatients, while prior studies evaluated (in part or completely) inpatient populations, who

typically present with more severe illness. Regardless, the risks of corticosteroid use and ED visits were higher in our outpatient opioid users, even those on short courses of opioids. Thus, opioid use is linked to unfavorable health outcomes in patients with IBD (even when used in a nonhospital setting or on a short-term basis).

This study has several potential limitations. First, it was a retrospective analysis and is subject to sampling error and recall bias. The use of International Classification of Diseases-10 codes is subject to coding errors, including incorrectly entered diagnoses. Second, sample sizes varied widely among the opioid use and nonuse cohorts. This may have skewed the results in unanticipated ways. Third, by excluding inpatients, we likely significantly reduced the number of individuals who underwent IBD-related surgery or experienced IBD-related complications or death. Finally, while the propensity score matching process was relatively extensive, it was not all encompassing, opening up the possibility of unrecognized sources of bias.

In spite of these issues, this study demonstrates that prescribing opioids to IBD outpatients carries significant, specific risks, regardless of prescription length. Healthcare professionals should exercise caution before prescribing these agents. These findings also reinforce the importance of using screening tools to identify individuals at risk of opioid use, as well as the ongoing need to develop safer visceral analgesic therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Transparency Statement:

Data that support this study are available from the TriNetX Diamond Network (www.trinetx.com).

Abbreviations:

IBD	inflammatory bowel disease
CI	confidence interval

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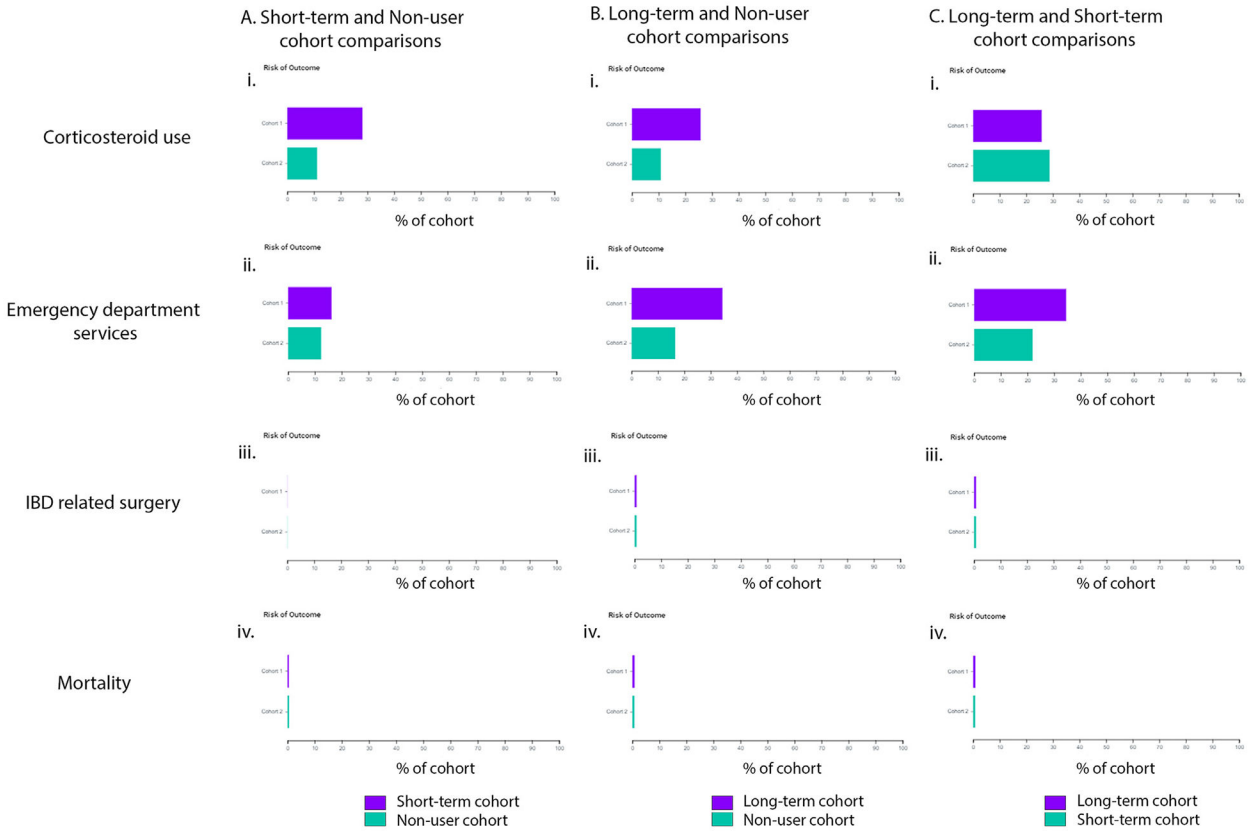

Figure.

Risk of outcome analysis: (A) Short-term and nonuser cohort comparisons i. Corticosteroid use, ii. Emergency department services, iii. IBD-related surgery, iv. Mortality; (B) Long-term and nonuser cohort comparisons i. Corticosteroid use, ii. Emergency department services, iii. IBD-related surgery, iv. Mortality; (C) Long-term and short-term cohort comparisons i. Corticosteroid use, ii. Emergency department services, iii. IBD-related surgery, iv. Mortality. Graphics used in this publication were downloaded from TriNetX and are permitted for use without express consent from TriNetX.