*Annals of Gastroenterology* (2023) **36,** 1-7

# Polysubstance use in inflammatory bowel disease is associated with increased risk of emergency department visits: a longitudinal study

**Kaleb Bogale[a], Izabela Zubrzycka[b], August Stuart[c], Melissa Cesaire[d], Vonn Walter[e], Andrew Tinsley[c], Emmanuelle Williams[c], Kofi Clarke[c], Matthew D. Coates[c,f]**

Columbia University Irving Medical Center, NY; Pennsylvania State University College of Medicine, Hershey, PA; Pennsylvania State University, Harrisburg, PA, USA

## Abstract

**Background** Polysubstance use (PSU), the simultaneous use of 2 or more substances of abuse, is common in inflammatory bowel disease (IBD). Preliminary studies suggest it may be associated with poor outcomes. This prospective study evaluated the impact of PSU on disease activity and healthcare resource utilization in IBD.

**Methods** This study was conducted in a tertiary IBD center between October 29, 2015, and December 31, 2019. Participants were assessed over 2 time points (index and follow-up outpatient appointments) separated by a minimum of 6 months. Demographics, endoscopic disease activity, and surveys assessing symptoms, healthcare resource utilization and substance use (tobacco, alcohol, marijuana, cocaine, methamphetamine, heroin, opioid, or benzodiazepine) were abstracted. We identified PSU during the index appointment and computed descriptive statistics and contingency table analyses, and multivariate logistic regression models at follow up to evaluate outcomes.

**Results** 162 consecutively enrolled IBD patients were included. Seventy-five patients (46%) were polysubstance users at the index appointment. The most common cohorts were utilizing tobacco and alcohol (n=40) or tobacco and opioids (n=13). On bivariate and multivariate analyses, PSU during the index visit was positively associated with emergency department (ED) visits (odds ratio [OR] 2.51, 95% confidence interval [CI] 1.24-5.07; P=0.01) and negatively associated with extraintestinal manifestations (OR 0.37, 95%CI 0.18-0.74; P=0.005). Age, sex, disease activity, disease subtype and IBD-related symptoms were not associated with PSU.

**Conclusions** IBD patients exhibiting PSU had increased risk of future ED visits. This study highlights the risks of PSU and reinforces the importance of appropriate substance use screening.

**Keywords** Inflammatory bowel disease, polysubstance use, healthcare resource utilization

*Ann Gastroenterol 2023; 36 (6): 1-7*

Correspondence to: Matthew D. Coates, MD, PhD, Associate Professor of Medicine, Penn State University Hershey Medical Center, Division of Gastroenterology and Hepatology, 500 University Drive, M.C. HU33, Hershey, PA 17033, USA, e-mail: mcoates@pennstatehealth.psu.edu

Received 16 April 2023; accepted 15 September 2023; published online 30 October 2023

DOI: https://doi.org/10.20524/aog.2023.0835



## Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic disorders of the gastrointestinal tract that may also be associated with substance use disorders [1]. IBD patients frequently use substances of abuse, and these agents have been associated with deleterious consequences and outcomes in this setting. For example, opioid use is common in IBD, with an estimated 50% of non-hospitalized adults and nearly 70% of hospitalized adults having been prescribed these medications [2,3]. This is important, as opioids have been associated with negative gastrointestinal clinical outcomes [4,5] and greater healthcare resource utilization

(HRU) [6-8], as expressed by hospitalization duration [9], readmissions [10] and emergency department (ED) visits [8]. Alcohol use in IBD is also common, and is associated with worsening gastrointestinal symptoms and greater frequency of relapsing disease [11-13]. Tobacco use in IBD is associated with more severe disease, particularly in the setting of Crohn's disease [14,15]. Cannabis use is increasingly common among IBD patients, but has recently been linked to higher rates of surgery in CD and a greater risk of substance misuse in this context [16,17].

Previous studies have also demonstrated that IBD patients often use 2 or more substances of abuse; this is known as polysubstance use (PSU) [18,19]. Risk factors for PSU in the general population include symptoms of anxiety or depression, negative mood dysregulation, comorbid psychiatric illness, and low socioeconomic status resulting in negative outcomes such as premature death [20-23]. We recently completed a retrospective, cross-sectional study in an IBD cohort that suggested that PSU was associated with increased risk for HRU [18]. However, no previous study has evaluated the long-term impact of PSU on clinical outcomes in IBD. We undertook a prospective study to further evaluate clinical and epidemiological associations with PSU in IBD, and to investigate the longitudinal impact of PSU in this setting.

## Patients and methods

### Study population

We performed a prospective analysis using data derived from encounters at the Penn State IBD Center, a single tertiary care center in Pennsylvania. This center includes a single specialty clinic with 4 gastroenterologists who specialize in the management of IBD. These encounters occurred between 29th October, 2015, and 31st December, 2019. This study was performed in accordance with the ethical standards described in the 1964 Declaration of Helsinki and its later amendments. It was approved by the Institutional Review Board and carried out under the protocol *#00013788*.

[a]Department of Medicine, Columbia University Irving Medical Center, New York (Kaleb Bogale); [b]Department of Medicine, Pennsylvania State University College of Medicine, Hershey, PA (Izabela Zubrzycka); [c]Department of Medicine, Division of Gastroenterology and Hepatology, Pennsylvania State University College of Medicine, Hershey, PA (August Stuart, Andrew Tinsley, Emmanuelle Williams, Kofi Clarke, Matthew D. Coates); [d]Department of Biological Sciences, Pennsylvania State University, Harrisburg, PA (Melissa Cesaire); [e]Department of Public Health Sciences and Department of Biochemistry, Pennsylvania State University College of Medicine, Hershey, PA (Vonn Walter); [f]Department of Pharmacology, Pennsylvania State University, Hershey, PA (Matthew D. Coates); USA

Conflict of Interest: None

Funding: This work was supported by the National Institutes of Health (NIH) National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (R01 DK122364), the Peter & Marshia Carlino Endowment in Inflammatory Bowel Disease [MDC] and the Margo E. Walrath Career Development Professorship in Gastroenterology [MDC]

The inclusion criteria were as follows: 1) all participants had to be assessed over 2 time points (index and follow up outpatient clinic visits) separated by a minimum of 6 months; and 2) all participants were over 17 years old with an established diagnosis of CD, UC, or IBD colitis of indeterminant nature based on standard clinical criteria routinely used to identify IBD [24], with ileocolonoscopic examination to identify the disease distribution. It should be noted that a majority of the patients we care for at this Center are CD (likely related to our status as a tertiary care and IBD referral center).

All participants were assessed at 2 time points (index and follow-up outpatient clinic visits), separated by a minimum of 6 months. Participants completed numerous contemporaneous surveys, including substance use questionnaires and IBD-related symptom assessments (including abdominal pain, fatigue, anxiety/depression, gas, diarrhea, tenesmus, rectal bleeding, and fecal urgency) such as the Harvey-Bradshaw Index (HBI), Simple Clinical Colitis Activity Index (SCCAI), and Hospital Anxiety and Depression Scale (HADS). Participants who exhibited new PSU (as defined below) during the observation period after the index appointment were excluded.

### Definitions and data extraction

PSU was defined as concurrent active or very recent use (within the prior week) of 2 or more non-prescription drugs or substances of abuse (specifically including tobacco, alcohol, marijuana, cocaine, methamphetamines, heroin, other opioids, or benzodiazepines) reported during the index appointment. Study participants responded to a comprehensive survey during their index clinic appointment to identify active or very recent substance use: (a) "Do you smoke or vape tobacco?" (participants could answer yes/no); (b) "Have you consumed alcohol in the past week?" (participants could answer yes/no); and (c) "Have you used any of the following substances in the past week?" (choices included marijuana/cannabis, cocaine, methamphetamines, heroin, and others; answers were yes/no).

At the follow-up visit, any IBD-related ED visits, hospitalization, imaging study or surgery within the previous 6 months were recorded. It should be noted that we did not include exam under anesthesia, perianal fistulotomies or abdominal surgeries immediately following the index encounter (i.e., surgeries that had been planned before the index encounter). IBD activity was determined based upon a direct ileocolonoscopic evaluation performed within 1 month of the follow-up appointment. In CD, endoscopically-confirmed disease activity was assessed with the simple endoscopic score for CD (SES-CD): 0-2, remission; 3-6, mild endoscopic activity; 7-15, moderate endoscopic activity; and over 15, severe endoscopic activity. Moderate-to-severe disease activity in CD was defined as an SES-CD score ≥7. UC was assessed with the Mayo endoscopy subscore, which ranges from 0 (no disease) to 3 (severe disease). Thus, moderate-to-severe disease activity in UC was defined as a Mayo endoscopy sub score of 2 or 3.

Additionally, we abstracted relevant demographic and clinical characteristics, including patient age, sex, duration of IBD, IBD extent/location, disease complications (previous or current gastrointestinal stricture, intra-abdominal fistula, abscess, or cancer development), surgical history, and current medications (including mesalamine, immunomodulator, biologic, antidepressant or anxiolytic, corticosteroid, and nonsteroidal anti-inflammatory druge usage).

### Statistical analysis

Data were extracted and analyzed using GraphPad Prism version 9 (GraphPad Software, San Diego, CA, USA) or R 4.0.5 (R Foundation for Statistical Computing, Vienna Austria). We identified PSU during the index appointment and computed descriptive statistics and contingency table analyses (e.g., Student's *t*-test for continuous variables and chi-square or Fisher's exact test for categorical variables, as appropriate) during the follow-up appointment, in order to compare the clinical outcomes between 2 cohorts: 1) patients with IBD reporting PSU at the index appointment; and 2) patients with IBD not reporting PSU (Fig. 1). We then created a multivariate logistic regression model incorporating age, sex, and all variables found to be significantly ($P<0.05$) or marginally significantly ($P=0.05$-$0.1$) associated with PSU in our aforementioned bivariate analysis. We reported odds ratios (ORs) and corresponding 95% confidence intervals (CIs) and considered P-values of $<0.05$ to be statistically significant.

## Results

### Study participant characteristics at index visit

A total of 162 IBD patients met the inclusion criteria for this study. This cohort included 99 females and 63 males, and had a mean age of 44 years, ranging from 20-82 years. Of these individuals, 115 were diagnosed with CD, 45 had UC, and 2 were described as having IBD colitis of indeterminate nature. At the index appointment, IBD-related medication use varied and included mesalamine (n=61, 38%), immunomodulators (n=44, 27%), biologics (n=78, 48%), steroids (n=51, 31%), and antibiotics (n=32, 20%). Patients reported symptoms that included fatigue (n=133, 82%), fecal urgency (n=109, 67%), abdominal pain (n=98, 60%), tenesmus (n=77, 48%), and rectal bleeding (n=52, 32%). Some patients also reported symptoms that were consistent with an anxious state (n=63, 39%) and/or depressive state (n=45, 28%), and/or utilized antidepressant or anxiolytic medication (n=45, 28%).

### Study participant characteristics at follow-up visit

At the follow-up appointment, the IBD-related medication use described included mesalamine (n=41, 25%), immunomodulators (n=43, 27%), biologics (n=103, 64%), steroids (n=41, 25%), and antibiotics (n=23, 14%). Study participants reported symptoms that included fatigue (n=137, 85%), fecal urgency (n=106, 65%), abdominal pain (n=97, 60%), tenesmus (n=68, 42%), and rectal bleeding (n=48, 30%) (Table 1). They also reported similar rates of experiencing an anxious state (n=61, 38%) or depressive state (n=37, 23%), and/or use of antidepressants or anxiolytics (n=60, 37%) (Table 1). There were 47 patients (29%) with moderate-to-severe disease activity and 90 patients (56%) with current or prior extraintestinal manifestations (Table 1). The median time to follow up was 15.8 months, with similar rates among the PSU cohort (16.4 months) and non-PSU cohort (14.1 months).

### Substance use in IBD

Sixty-eight patients (42%) reported single substance use: tobacco (n=57, 84%), heroin (n=6, 9%), marijuana (n=2, 3%), non-heroin opioids (n=2, 3%) or alcohol (n=1, 1%). Nineteen (12%) reported no substance use. Seventy-five patients (46%) reported PSU at the time of the index visit. Of these, 62 used 2 substances, 12 used 3 substances and 1 used 5 substances. The rates of individual substance use in PSU were as follows: tobacco (n=73, 97%), alcohol (n=53, 71%), non-heroin opioids (n=24, 32%), marijuana (n=12, 16%), and heroin (n=3, 4%). No patient reported using cocaine or methamphetamine. The most common cohorts with PSU were using tobacco and alcohol (n=40), tobacco and opiates (n=13), tobacco, opiates and alcohol (n=8), or tobacco and marijuana (n=6). The rate of tobacco use in the PSU group (97%) was similar to that in the non-PSU patients (84%).

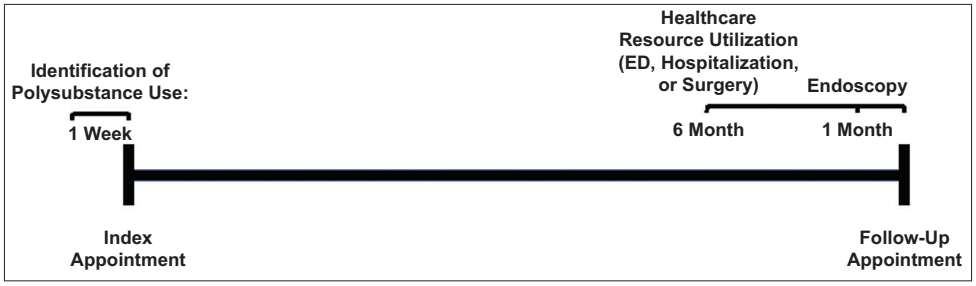


**Figure 1** Timelines associated with the study design
*ED, emergency department*

**Table 1** Follow-up appointment, clinical characteristics and outcomes

| Variable | Total (n=162) | PSU (n=75) | No PSU (n=87) | Odds ratio | 95%CI | | P-value |
|---|---|---|---|---|---|---|---|
| Age (mean years) | 44.0 | 43.9 | 44.0 | | | | 0.44 |
| Female sex (%) | 99 (61%) | 45 (60%) | 54 (62%) | 1.09 | 0.58 | 2.05 | 0.87 |
| Time of follow up (median months) | 15.8 | 16.4 | 14.1 | | | | 0.14 |
| IBD subtype (CD/UC) | 115/45 | 51/23 | 64/22 | 0.76 | 0.38 | 1.52 | 0.48 |
| Moderate or severe inflammation (%) (on endoscopic evaluation) | 47 (29%) | 17 (23%) | 30 (34%) | 0.56 | 0.28 | 1.09 | 0.12 |
| Extra-intestinal manifestations (current or prior) (%) | 90 (56%) | 32 (43%) | 58 (67%) | 0.37 | 0.20 | 0.69 | 0.0026 |
| Depression (%) | 37 (23%) | 18 (24%) | 19 (22%) | 1.13 | 0.55 | 2.30 | 0.85 |
| Anxiety (%) | 61 (38%) | 30 (40%) | 31 (36%) | 1.20 | 0.64 | 2.28 | 0.63 |
| Antidepressant or anxiolytic use (%) | 60 (37%) | 34 (45%) | 26 (30%) | 1.95 | 1.02 | 3.64 | 0.051 |
| Steroid use (%) | 41 (25%) | 17 (23%) | 24 (28%) | 0.77 | 0.38 | 1.58 | 0.59 |
| Antibiotic use (%) | 23 (14%) | 16 (21%) | 7 (8%) | 3.10 | 1.19 | 7.83 | 0.023 |
| Mesalamine use (%) | 41 (25%) | 17 (23%) | 24 (28%) | 0.77 | 0.38 | 1.58 | 0.59 |
| Immunomodulator use (%) | 43 (27%) | 14 (19%) | 29 (33%) | 0.46 | 0.23 | 0.95 | 0.049 |
| Biologic use (%) | 103 (64%) | 52 (69%) | 51 (59%) | 1.60 | 0.84 | 2.98 | 0.19 |
| Emergency department (%) | 91 (56%) | 51 (68%) | 40 (46%) | 2.50 | 1.34 | 4.61 | 0.0068 |
| Hospitalization (%) | 71 (44%) | 36 (48%) | 33 (38%) | 1.51 | 0.82 | 2.82 | 0.21 |
| Surgery (%) | 62 (38%) | 28 (37%) | 34 (39%) | 0.93 | 0.49 | 1.74 | 0.87 |
| Imaging studies (%) | 114 (70%) | 57 (76%) | 57 (66%) | 1.67 | 0.86 | 3.23 | 0.17 |
| Fatigue (%) | 137 (85%) | 65 (87%) | 72 (83%) | 1.35 | 0.57 | 3.24 | 0.52 |
| Abdominal pain (%) | 97 (60%) | 40 (53%) | 57 (66%) | 0.60 | 0.32 | 1.12 | 0.15 |
| Tenesmus (%) | 68 (42%) | 29 (39%) | 39 (45%) | 0.78 | 0.41 | 1.43 | 0.52 |
| Fecal urgency (%) | 106 (65%) | 48 (64%) | 58 (67%) | 0.89 | 0.46 | 1.73 | 0.74 |
| Rectal bleeding (%) | 48 (30%) | 20 (27%) | 28 (32%) | 0.77 | 0.38 | 1.47 | 0.49 |

All medication use referred to above is that described at the time of the follow-up visit
*PSU, polysubstance abuse; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; CI, confidence interval*

On bivariate analysis, PSU at index appointment was positively associated with antibiotic use (OR 3.1, 95%CI 1.19-7.83) at the follow-up appointment, while immunomodulator use (OR 0.46, 95%CI 0.23-0.95) was negatively associated (Table 1). There was no association between PSU and other IBD medications, such as biologics, steroids or mesalamine (Table 1). Extra-intestinal manifestations were negatively associated with PSU in bivariate and multivariate analyses (Table 1). Age, sex, disease activity, disease subtype or IBD-related symptoms were not associated with PSU (Table 1). A subset analysis, comparing single substance and no substance use, demonstrated there were no significant differences in demographics (age or sex), disease subtype, disease activity or disease complications (Supplementary Table 1).

### HRU in IBD

In between the index and follow-up appointments, varying numbers of the study participants underwent IBD-related imaging tests (n=114, 70%), visited the ED (n=91, 56%), were hospitalized (n=71, 44%), and/or underwent IBD-related surgery (n=62, 38%) (Table 1). PSU during the index appointment was positively associated with ED visits on bivariate (OR 2.50, 95%CI 1.34-4.61) and multivariate analysis (OR 2.51, 95%CI 1.24-5.07) (Tables 1, 2). The relative rate of ED visits among the PSU group (n=51, 68%) was significantly higher than that in the non-PSU group (n=40, 46%) (P=0.0068) (Fig. 2). Otherwise, there was no relationship between PSU and other types of HRU, including hospitalizations, surgery or imaging studies (Fig. 2). A subset analysis, comparing single substance and no substance use, demonstrated there were no differences in HRU (hospitalizations, ED visits or surgery) (Supplementary Table 1).

## Discussion

In this prospective study evaluating the impact of PSU on clinical outcomes in IBD, we demonstrated that PSU is

**Table 2** Multivariate logistic regression model, showing associations with polysubstance use in inflammatory bowel disease

| Variable | Odds ratio | 95%CI | | P-value |
|---|---|---|---|---|
| Age | 0.99 | 0.98 | 1.02 | 0.92 |
| Female sex | 0.90 | 0.44 | 1.83 | 0.77 |
| Extra-intestinal manifestations (present or prior) | 0.37 | 0.18 | 0.74 | 0.0048 |
| Antibiotic use | 2.81 | 0.99 | 7.96 | 0.052 |
| Immunomodulator use | 0.47 | 0.21 | 1.03 | 0.059 |
| Antidepressant use | 1.7 | 0.84 | 3.47 | 0.14 |
| Emergency department use | 2.51 | 1.24 | 5.07 | 0.01 |

*CI, confidence interval*

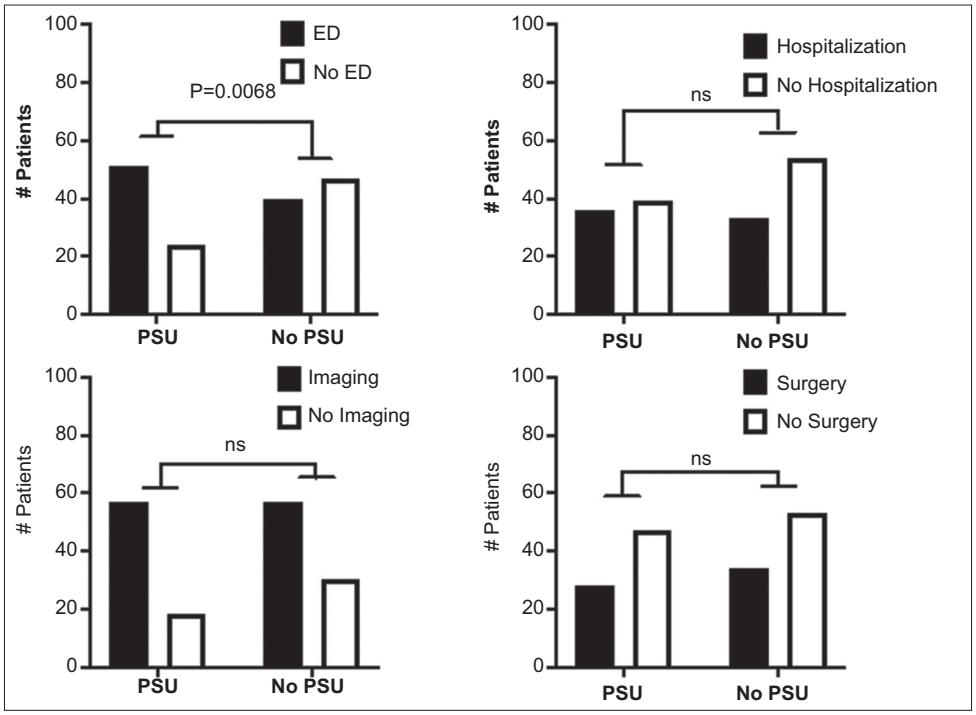


**Figure 2** Patterns of healthcare resource utilization in polysubstance use
*PSU, polysubstance abuse; ED, emergency department*

common in this setting, being reported by 46% of patients at the index appointment. This is similar to the findings of previous investigations, including one of our own. Notably, PSU during the index appointment was positively associated with future ED visits. Antibiotic use was positively associated with PSU on bivariate analysis, while immunomodulator use was negatively associated. However, there was no association with any medications when confounding variables were accounted for in the multivariate logistic regression model. Interestingly, PSU was negatively associated with previous or current extra-intestinal manifestations of IBD.

The principal finding in this report was the association between PSU and future ED visits. This contrasts with our previous cross-sectional study evaluating PSU in IBD, where the healthcare resource associated with PSU was imaging services [18]. Thus, the association between PSU and ED visits demonstrated in the present study was relatively novel. It should be noted that we reported a similar overall rate of ED visits (56%) to some previous studies [25], whereas other reports suggested a lower rate [26]. Previously identified risk factors for ED visits in IBD include opioid use, more comorbidities, psychiatric illness, anemia and a greater number of previous IBD-related hospitalizations [25,27,28]. This is important, as recent longitudinal studies have demonstrated that the rates of ED visits in IBD cohorts have continued to increase annually [29,30]. We reported an overall rate of hospitalizations of 44%, and we did not identify a relationship with PSU. National estimates of hospitalizations in IBD are lower than our reported rate, with a higher rate among patients with CD, although overall hospitalization rates are stable in industrialized nations [26,31].

Notably, there was no association between PSU and endoscopically-confirmed IBD disease activity in this study, similarly to our previous retrospective study [18]. No previous studies were specifically designed to evaluate the longitudinal impact of PSU on IBD disease activity with endoscopic evaluation, which prompted this current study. Although a previous investigation did show an association between PSU and disease activity among the adolescent and young adult population, disease activity was not endoscopically confirmed or determined with validated surveys (HBI and SCCAI) [19]. Anxiety as a driver of ED presentations was considered and evaluated; however, reports of anxiety in this cohort were no greater than in previous studies. Nevertheless, our study demonstrated a higher rate of ED visits, which persisted even in the absence of greater disease activity or more symptoms of IBD.

Several types of intervention have demonstrated promise in regard to decreasing the rate of HRU in IBD, including interdisciplinary care teams and clinical care pathways [32-34], specialized inpatient IBD care teams [35], digital health interventions [36], and the integration of psychiatric care in IBD specialty clinics [37-39]. A cost-benefit analysis for the integration of a psychological care model alone, which has previously been shown to be effective in the ambulatory setting [40], suggests net savings of $58,647 over 2 years [37]. Overall, these efforts to decrease HRU in IBD have previously been most successful when targeted at the IBD patients who have the highest risk of needing HRU [38,39]. Our present study provides further evidence that screening for substance abuse and/or polysubstance abuse could also serve as a relatively low-cost intervention to reduce HRU in IBD.

There were limitations to this study. As in other reports on substance use, we utilized patient-reported data that may be underestimating the true rate of PSU, as well as some of the key outcomes measured, including HRU [41]. The laboratory values gathered were not available for all participants, so we were unable to assess the impact of potentially relevant markers, such as hemoglobin or inflammatory markers (erythrocyte sedimentation rate and C-reactive protein). There were also fewer total participants in this prospective study (N=162) than in our previous cross-sectional analysis (N=361), which limited our ability to conduct further refined analysis comparing PSU in CD and UC. Finally, we were unable to gather reliable data related to substance dose and frequency of use. Thus, we could not perform an analysis to evaluate for a potential dose–response effect from 1 or more substances.

In summary, this study reinforces the significant impact of PSU in IBD. Individuals with IBD have a higher risk for PSU, and this behavior is associated with a greater likelihood of HRU. These findings provide further evidence for the importance of screening IBD patients for PSU, and counseling patients to limit substance use in this setting.

**Summary Box**

**What is already known:**

- Patients with inflammatory bowel disease (IBD) frequently use 2 or more substances of abuse (polysubstance use [PSU])
- In a recent retrospective study, PSU was associated with greater healthcare resource utilization

**What the new findings are:**

- This prospective study was undertaken to more carefully evaluate risk factors and impacts of PSU in this setting
- PSU was inversely associated with extraintestinal manifestations
- Polysubstance users were more likely to require emergency department visits
- This study highlights the negative impacts of PSU and reinforces the importance of screening for it in IBD patients

## References

1. Carney H, Marrie RA, Bolton JM, et al. Prevalence and risk factors of substance use disorder in inflammatory bowel disease. *Inflamm Bowel Dis* 2021;**27**:58-64.
2. Szigethy E, Knisely M, Drossman D. Opioid misuse in gastroenterology and non-opioid management of abdominal pain. *Nat Rev Gastroenterol Hepatol* 2018;**15**:168-180.
3. Buckley JP, Kappelman MD, Allen JK, Van Meter SA, Cook SF. The burden of comedication among patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013;**19**:2725-2736.
4. Targownik LE, Nugent Z, Singh H, Bugden S, Bernstein CN. The prevalence and predictors of opioid use in inflammatory bowel disease: a population-based analysis. *Am J Gastroenterol* 2014;**109**:1613-1620.
5. Hanson KA, Loftus EV Jr, Harmsen WS, Diehl NN, Zinsmeister AR, Sandborn WJ. Clinical features and outcome of patients with inflammatory bowel disease who use narcotics: a case-control study. *Inflamm Bowel Dis* 2009;**15**:772-777.
6. Szigethy EM, Murphy SM, Ehrlich OG, et al. Opioid use associated with higher costs among patients with inflammatory bowel disease. *Crohns Colitis 360* 2021;**3**:otab021.
7. Sheehan JL, Jacob J, Berinstein EM, et al. The relationship between opioid use and healthcare utilization in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis* 2022;**28**:1904-1914.
8. Alley K, Singla A, Afzali A. Opioid use is associated with higher health care costs and emergency encounters in inflammatory bowel disease. *Inflamm Bowel Dis* 2019;**25**:1990-1995.
9. Cohen-Mekelburg S, Rosenblatt R, Gold S, et al. The impact of opioid epidemic trends on hospitalised inflammatory bowel disease patients. *J Crohns Colitis* 2018;**12**:1030-1035.
10. Charilaou P, Mohapatra S, Joshi T, et al. Opioid use disorder

increases 30-day readmission risk in inflammatory bowel disease hospitalizations: a nationwide matched analysis. *J Crohns Colitis* 2020;**14**:636-645.
11. Rungoe C, Basit S, Ranthe MF, Wohlfahrt J, Langholz E, Jess T. Risk of ischaemic heart disease in patients with inflammatory bowel disease: a nationwide Danish cohort study. *Gut* 2013;**62**:689-694.
12. Haapamäki J, Roine RP, Turunen U, Färkkilä MA, Arkkila PE. Increased risk for coronary heart disease, asthma, and connective tissue diseases in inflammatory bowel disease. *J Crohns Colitis* 2011;**5**:41-47.
13. Cohen AB, Lee D, Long MD, et al. Dietary patterns and self-reported associations of diet with symptoms of inflammatory bowel disease. *Dig Dis Sci* 2013;**58**:1322-1328.
14. Picco MF, Bayless TM. Tobacco consumption and disease duration are associated with fistulizing and stricturing behaviors in the first 8 years of Crohn's disease. *Am J Gastroenterol* 2003;**98**:363-368.
15. Cosnes J, Carbonnel F, Beaugerie L, Le Quintrec Y, Gendre JP. Effects of cigarette smoking on the long-term course of Crohn's disease. *Gastroenterology* 1996;**110**:424-431.
16. Bogale K, Raup-Konsavage W, Dalessio S, Vrana K, Coates MD. Cannabis and cannabis derivatives for abdominal pain management in inflammatory bowel disease. *Med Cannabis Cannabinoids* 2021;**4**:97-106.
17. Hansen TM, Sabourin BC, Oketola B, Bernstein CN, Singh H, Targownik LE. Cannabis use in persons with inflammatory bowel disease and vulnerability to substance misuse. *Inflamm Bowel Dis* 2020;**26**:1401-1406.
18. Bogale K, Vrana K, Konsavage WR, et al. Polysubstance use in inflammatory bowel disease. *J Dig Dis* 2021;**22**:706-713.
19. Plevinsky JM, Maddux MH, Greenley RN. Substance use in adolescents and young adults with inflammatory bowel diseases: an exploratory cluster analysis. *J Pediatr Gastroenterol Nutr* 2019;**69**:324-329.
20. Redonnet B, Chollet A, Fombonne E, Bowes L, Melchior M. Tobacco, alcohol, cannabis and other illegal drug use among young adults: the socioeconomic context. *Drug Alcohol Depend* 2012;**121**:231-239.
21. Schuckit MA. Comorbidity between substance use disorders and psychiatric conditions. *Addiction* 2006;**101**(Suppl 1):76-88.
22. Crane NA, Langenecker SA, Mermelstein RJ. Risk factors for alcohol, marijuana, and cigarette polysubstance use during adolescence and young adulthood: A 7-year longitudinal study of youth at high risk for smoking escalation. *Addict Behav* 2021;**119**:106944.
23. Hjemsæter AJ, Bramness JG, Drake R, et al. Mortality, cause of death and risk factors in patients with alcohol use disorder alone or poly-substance use disorders: a 19-year prospective cohort study. *BMC Psychiatry* 2019;**19**:101.
24. Sands BE. From symptom to diagnosis: clinical distinctions among various forms of intestinal inflammation. *Gastroenterology* 2004;**126**:1518-1532.
25. Nugent Z, Singh H, Targownik LE, Strome T, Snider C, Bernstein CN. Predictors of emergency department use by persons with inflammatory bowel diseases: a population-based study. *Inflamm Bowel Dis* 2016;**22**:2907-2916.
26. Kappelman MD, Porter CQ, Galanko JA, et al. Utilization of healthcare resources by U.S. children and adults with inflammatory bowel disease. *Inflamm Bowel Dis* 2011;**17**:62-68.
27. Limsrivilai J, Stidham RW, Govani SM, Waljee AK, Huang W, Higgins PD. Factors that predict high health care utilization and costs for patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2017;**15**:385-392.
28. Dubinsky MC, Dotan I, Rubin DT, et al. Burden of comorbid anxiety and depression in patients with inflammatory bowel disease: a systematic literature review. *Expert Rev Gastroenterol Hepatol* 2021;**15**:985-997.
29. Ballou S, Hirsch W, Singh P, et al. Emergency department utilisation for inflammatory bowel disease in the United States from 2006 to 2014. *Aliment Pharmacol Ther* 2018;**47**:913-921.
30. Ananthakrishnan AN, McGinley EL, Saeian K, Binion DG. Trends in ambulatory and emergency room visits for inflammatory bowel diseases in the United States: 1994-2005. *Am J Gastroenterol* 2010;**105**:363-370.
31. Buie MJ, Quan J, Windsor JW, et al; Global IBD Visualization of Epidemiology Studies in the 21st Century (GIVES-21) Research Group. Global hospitalization trends for Crohn's disease and ulcerative colitis in the 21st century: a systematic review with temporal analyses. *Clin Gastroenterol Hepatol* 2023;**21**:2211-2221.
32. Lytvyak E, Sutton RT, Dieleman LA, Peerani F, Fedorak RN, Kroeker KI. Management of inflammatory bowel disease patients with clinical care pathways reduces emergency department utilization. *Crohns Colitis 360* 2020;**2**:otaa080.
33. Liu JJ, Rosson TB, Xie JJ, et al. Personalized inflammatory bowel disease care reduced hospitalizations. *Dig Dis Sci* 2019;**64**:1809-1814.
34. Regueiro M, Click B, Anderson A, et al. Reduced unplanned care and disease activity and increased quality of life after patient enrollment in an inflammatory bowel disease medical home. *Clin Gastroenterol Hepatol* 2018;**16**:1777-1785.
35. Hong SJ, Jang J, Berg D, et al. Implementation of an inpatient IBD service is associated with improvement in quality of care and long-term outcomes. *Dig Dis Sci* 2021;**66**:3753-3759.
36. Zhen J, Marshall JK, Nguyen GC, Atreja A, Narula N. Impact of digital health monitoring in the management of inflammatory bowel disease. *J Med Syst* 2021;**45**:23.
37. Lores T, Goess C, Mikocka-Walus A, et al. Integrated psychological care reduces health care costs at a hospital-based inflammatory bowel disease service. *Clin Gastroenterol Hepatol* 2021;**19**:96-103.
38. Fudman DI, Perez-Reyes AE, Niccum BA, Melmed GY, Khalili H. Interventions to decrease unplanned healthcare utilization and improve quality of care in adults with inflammatory bowel disease: a systematic review. *Clin Gastroenterol Hepatol* 2022;**20**:1947-1970.
39. Keefer L, Gorbenko K, Siganporia T, et al. Resilience-based integrated IBD care is associated with reductions in health care use and opioids. *Clin Gastroenterol Hepatol* 2022;**20**:1831-1838.
40. Bogale K, Yadav S, Stuart A, et al. Dedicated psychiatry clinic for inflammatory bowel disease patients has a positive impact on depression scores. *Inflamm Intest Dis* 2022;**7**:81-86.
41. Morral AR, McCaffrey D, Iguchi MY. Hardcore drug users claim to be occasional users: drug use frequency underreporting. *Drug Alcohol Depend* 2000;**57**:193-202.

## Supplementary

**Supplementary** Table 1 Follow-up appointment, subset analysis of non-PSU cohort

| Variable | Total (n=87) | Single substance (n=68) | No substance (n=19) | Odds ratio | 95%CI | | P-value |
|---|---|---|---|---|---|---|---|
| Age (mean years) | 44.0 | 42.8 | 48.2 | | | | 0.17 |
| Female sex (%) | 54 | 41 | 13 | 0.70 | 0.23 | 2.16 | 0.60 |
| Time of follow up (median months) | 14.1 | 16.8 | 12.1 | | | | 0.15 |
| IBD subtype (CD/UC) | 64/22 | 51/16 | 13/6 | 1.47 | 0.46 | 4.28 | 0.56 |
| Moderate or severe inflammation (%) (on endoscopic evaluation) | 30 | 22 | 8 | 0.66 | 0.25 | 1.97 | 0.43 |
| Extra-intestinal manifestations (current or prior) (%) | 58 | 46 | 12 | 1.22 | 0.46 | 3.26 | 0.79 |
| Depression (%) | 19 | 14 | 5 | 0.73 | 0.23 | 2.12 | 0.75 |
| Anxiety (%) | 31 | 22 | 9 | 0.53 | 0.19 | 1.48 | 0.28 |
| Antidepressant or anxiolytic use (%) | 26 | 17 | 9 | 0.37 | 0.13 | 1.07 | 0.09 |
| Steroid use (%) | 24 | 19 | 5 | 1.09 | 0.37 | 3.04 | 0.99 |
| Antibiotic use (%) | 7 | 5 | 2 | 0.67 | 0.12 | 3.64 | 0.64 |
| Mesalamine use (%) | 24 | 22 | 2 | 4.07 | 0.93 | 18.8 | 0.08 |
| Immunomodulator use (%) | 29 | 20 | 9 | 0.46 | 0.17 | 1.31 | 0.17 |
| Biologic use (%) | 51 | 38 | 13 | 0.58 | 0.19 | 1.79 | 0.33 |
| Emergency department (%) | 40 | 29 | 11 | 0.54 | 0.18 | 1.44 | 0.30 |
| Hospitalization (%) | 33 | 24 | 9 | 0.61 | 0.23 | 1.68 | 0.42 |
| Surgery (%) | 34 | 25 | 9 | 0.65 | 0.24 | 1.78 | 0.43 |
| Imaging studies (%) | 57 | 44 | 13 | 0.85 | 0.28 | 2.38 | 0.99 |
| Fatigue (%) | 72 | 56 | 16 | 0.88 | 0.24 | 3.57 | 0.99 |
| Abdominal pain (%) | 57 | 42 | 15 | 0.43 | 0.14 | 1.31 | 0.19 |
| Tenesmus (%) | 39 | 32 | 7 | 1.52 | 0.51 | 3.96 | 0.60 |
| Fecal urgency (%) | 58 | 45 | 13 | 0.90 | 0.29 | 2.51 | 0.99 |
| Rectal bleeding (%) | 28 | 26 | 2 | 5.26 | 1.23 | 24.2 | 0.02 |

*PSU, polysubstance abuse; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; CI, confidence interval*