Prevalence and Risk Factors of Substance Use Disorder in Inflammatory Bowel Disease

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Background: Substance use disorders (SUDs) impose a substantial individual and societal burden; however, the prevalence and associated factors in persons with inflammatory bowel disease (IBD) are largely unknown. We evaluated the prevalence and risk factors of SUD in an IBD cohort.

Methods: Inflammatory bowel disease participants (n = 247) were recruited via hospital- and community-based gastroenterology clinics, a population-based IBD research registry, and primary care providers as part of a larger cohort study of psychiatric comorbidity in immune-mediated inflammatory diseases. The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders IV was administered to participants to identify lifetime SUD, anxiety disorder, and major depressive disorder. Additional questionnaires regarding participants' sociodemographic and clinical characteristics were also completed. We examined demographic and clinical factors associated with lifetime SUD using unadjusted and adjusted logistic regression modeling.

Results: Forty-one (16.6%) IBD participants met the criteria for a lifetime diagnosis of an SUD. Factors associated with elevated odds of SUD were ever smoking (adjusted odds ratio [aOR], 2.96; 95% confidence interval [CI], 1.17–7.50), male sex (aOR, 2.44; 95% CI, 1.11–5.36), lifetime anxiety disorder (aOR, 2.41; 95% CI, 1.08–5.37), and higher pain impact (aOR, 1.08; 95% CI, 1.01–1.16).

Conclusions: One in six persons with IBD experienced an SUD, suggesting that clinicians should maintain high index of suspicion regarding possible SUD, and inquiries about substance use should be a part of care for IBD patients, particularly for men, smokers, and patients with anxiety disorders and pain.

Key Words: inflammatory bowel disease, substance use disorders, SCID

INTRODUCTION

Psychiatric disorders are strongly associated with inflammatory bowel disease (IBD). Persons with IBD have over twice the odds of generalized anxiety disorder (AD) and major depressive disorder (MDD) compared with the general population.[1–3] However, there has been minimal investigation of substance use disorder (SUD) in those with IBD. Existing research regarding SUD in those with IBD has been limited to

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either specific subpopulations with IBD, including pregnant and postpartum women,[4] or has investigated self-reported substance use but not specialist- or interviewer-diagnosed SUD.[5–7] A review of studies examining alcohol use in IBD found a similar prevalence of alcohol consumption in those with IBD compared with the general population, and most studies identified an association between alcohol consumption and a worsening of IBD symptoms.[6]

Substance use disorder may complicate the management of IBD. Comorbid SUD and chronic conditions are associated with higher rates of hospitalization than chronic conditions alone,[8] and the presence of an SUD may interfere with adherence to treatment of the chronic condition and self-care behaviors.[8] The high prevalence of psychiatric disorders in IBD and the association between AD, mood disorders, and SUD in the general population,[9] suggest that persons with IBD may have an a relatively high prevalence of SUD. The prevalence and predictors of SUD in those with IBD are unknown. Therefore, we aimed to evaluate the frequency of and risk factors for SUD in those with IBD.

MATERIAL AND METHODS

Study Design

This study used data from the enrollment visit of a cohort study investigating psychiatric comorbidities in immune-mediated inflammatory diseases, as described elsewhere.[10] Briefly, between 2014 and 2016, the study recruited 247 individuals with IBD for a 3-year longitudinal study from various sites within the Canadian province of Manitoba.

Study Population

Participants with IBD, including Crohn's disease (CD) and ulcerative colitis (UC),[11, 12] were recruited via multiple routes to ensure broad representativeness, including hospital- and community-based gastroenterology clinics, a population-based IBD research registry, and primary care providers. Inflammatory bowel disease was confirmed by medical records review or through the treating physician. Participants were 18 years of age or older and able to provide informed consent.

Procedures

After providing consent, participants completed self-report questionnaires during their initial study visit that captured sociodemographic and clinical information. The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV (SCID) was administered in person or over the phone by a trained interviewer. As described elsewhere, interviewers included nurses, graduate students, and research coordinators who were trained by a registered clinical health psychologist, with regular review of fidelity to the interview method.[10]

Measures

Sociodemographic and clinical characteristic self-report questionnaires provided the following characteristics: age, sex, race, marital status, household income, highest level of education, and smoking history. Race was categorized as white or nonwhite, due to a limited number of nonwhite participants. Annual household income was grouped as "<$50,000," "≥$50,000," or "decline to answer" to ensure reasonable cell sizes. Highest level of education was dichotomized as "high school or below" and "above high school." Marital status was classified as "single" (including never married, divorced, widowed, separated) or "married/common-law." Participants reported current and past smoking behaviors; participants who reported having in their lifetime smoked ≥100 cigarettes were categorized as "ever smokers."[10] Self-reported, physician-diagnosed physical comorbidities (including cardiovascular diseases, diabetes mellitus, kidney disease, and cancers, among others) were recorded using a validated comorbidity questionnaire.[13] Pain impact was recorded using the Modified Medical Outcomes Study Pain Effects Scale, a valid, reliable tool derived from the Pain Effects Scale[14, 15] that includes a 6-item assessment of the effects of pain, defined as any unpleasant sensory symptom on mood and activities during the previous 4 weeks. Total scores range from 6 to 30, with higher scores indicating greater impact of pain. Though additional measures of different pain dimensions would have been useful, only a single measure was used to reduce participant burden.

IBD-specific Characteristics

Participants with IBD were subtyped as either ulcerative colitis or Crohn's disease. Age of IBD onset was characterized using the Montreal classification, which groups age of IBD onset as younger than 17, 17 to 40, and over 40 years of age.[11] Inflammatory bowel disease activity was assessed using validated clinical indices: for UC, using the Powell-Tuck Index, and for CD, using the Harvey-Bradshaw Index; scores ≥5 on both scales reflected symptomatically active disease.[16, 17]

Mental Disorders

Mental disorders were identified according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria, the prevailing diagnostic criteria at the time the study was designed, based on the participant's SCID. Substance use disorders were defined by meeting diagnostic criteria for current or lifetime SUD and categorized by DSM-IV diagnoses: alcohol abuse, alcohol dependence, drug abuse, and drug dependence. The following drugs were included in this definition: sedatives, hypnotics, anxiolytics, cannabis, stimulants, opioids, cocaine, hallucinogens, and other drugs (eg, steroids, solvents). Tobacco use was not included. We also summarized self-reported lifetime alcohol and substance use that did not meet DSM-IV diagnostic criteria, which we report here as "ever substance use."

Participants were classified as having an AD if they met diagnostic criteria for any current or lifetime AD. Anxiety classifications followed DSM-IV disorders: panic disorder, generalized anxiety disorder, agoraphobia without history of panic disorder, specific phobia, social phobia, AD due to a general medical condition, substance-induced AD, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD). Participants were categorized as having MDD if they met diagnostic criteria for current or lifetime MDD. Both current and lifetime AD and MDD were considered to allow for a greater understanding of the lifetime relationship between SUD and AD and/or MDD. Population-based studies have shown that the incidence and prevalence of bipolar disorder are higher in the IBD population than the non-IBD population, in the context of a low base rate overall.[18, 19] However, we did not include bipolar disorder due to the small number of affected participants in our cohort (n = 4, 1.6%).

Statistical Analysis

Participant characteristics were summarized for the full IBD cohort and then stratified by the presence or absence of SUD. We compared participants with and without SUD using descriptive statistics (χ^2 tests and Student *t* tests). The frequency and characteristics of current and lifetime SUD were summarized in the full IBD cohort.

We used binary logistic regression models to determine the association between various patient characteristics and SUD, with associations reported as unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs). The following factors were considered in the multivariable model for an association with SUD in IBD: sex, age, marital status, number of physical comorbidities, pain impact, smoking history, IBD subtype, SCID-diagnosed MDD, and SCID-diagnosed AD. The covariates were chosen either based on previously established associations with SUD (male, age, marital status, physical comorbidities, and pain)[8, 20–22] or if they reached a level of significance of $P \leq 0.05$ in unadjusted analysis. Inflammatory bowel disease subtype was also included as a covariate to investigate whether risk for SUD differs between CD and UC.

Complementary analyses

Given that DSM-5 has replaced DSM-IV since the study was designed, we repeated our logistic regression analyses characterizing AD in a way that more closely reflects the DSM-5 concept of an AD, which does not include OCD and PTSD.[23]

P values ≤0.05 were considered statistically significant. Analyses were performed using SPSS version 25 (IBM Corporation, Armonk, NY).

Ethical Considerations

The study was approved by the University of Manitoba Research Ethics Board.

RESULTS

Forty-one (16.6%) of 247 participants met the criteria for a SCID lifetime diagnosis of an SUD (Table 1). Alcohol abuse was the most common lifetime SUD diagnosis (9.3%), followed by alcohol dependence (7.3%) and drug abuse (7.3%, Table 2). Drug dependence was infrequent (3.6%). Participants with lifetime SUD had a higher prevalence of AD, higher prevalence of MDD, higher frequency of ever smoking, and higher pain impact compared with those without SUD (Table 1). Overall, a higher proportion of participants had Crohn's disease compared with ulcerative colitis (61.9% vs 38.1%). Most participants were female, white, had postsecondary education, and were ever smokers (51.0% of those with no SUD and 80.5% of those with SUD). Almost one third of participants with IBD met the criteria for a SCID lifetime diagnosis of an AD, and over one third of participants met SCID criteria for lifetime diagnosis of MDD.

In the univariate logistic regression analysis, several factors were significantly associated with meeting criteria for lifetime SUD, including lifetime AD, ever smoking, higher pain impact, and lifetime MDD (Fig. 1; see Supplementary Table 1, which contains the results of the logistic regression analyses). Multivariable logistic regression analysis subsequently revealed ever smoking (adjusted OR [aOR], 2.96; 95% CI, 1.17–7.50), male sex (aOR, 2.44; 95% CI, 1.11–5.36), lifetime AD (aOR, 2.41; 95% CI, 1.08–5.37), and higher pain impact (aOR, 1.08; 95% CI, 1.01–1.16; representing an 8% increase in the odds of SUD for each point on the pain scale) to be significantly associated with lifetime SUD in IBD (Fig. 1). Major depressive disorder was no longer associated with lifetime SUD upon adjustment for other covariates (aOR, 1.59; 95% CI, 0.69–3.67).

Upon applying the DSM-5 classification for AD, which does not include OCD or PTSD,[23] 65 (26.3%) participants from the IBD cohort met the criteria for a SCID lifetime diagnosis of an AD. After repeating the logistic regression analysis while applying the DSM-5 definition of AD, predictors of SUD in this model were similar in magnitude and direction as those predicting SUD when we applied the DSM-IV definition of AD (see Supplementary Table 2).

DISCUSSION

In this study, we examined prevalence and sociodemographic and clinical risk factors of SUD in IBD. To the best of our knowledge, this study represents one of the first to investigate the occurrence and predictors of SUD in those with IBD. We found that the lifetime prevalence of DSM-IV diagnosed alcohol abuse and dependence in those with IBD in general was lower than reported in the average American population (abuse, 9.3% in the current IBD cohort vs 17.8% general population; dependence, 7.3% vs 12.5%),[21] which may reflect an association between alcohol and worsening of IBD symptoms.[6] Although previous studies have reported the prevalence of alcohol consumption in those with IBD to be similar to

TABLE 1. Participant Characteristics of Those With Inflammatory Bowel Disease and Comorbid Substance Use Disorder

	(1) All IBD	(2) IBD/no SUD	(3) IBD/SUD	*P* (2) vs (3)
No.	247 (100%)	206 (83.4%)	41 (16.6%)	
Males, n (%)	92 (37.2)	72 (35.0)	20 (48.8)	0.09
Age,[a] median (IQR), years	48.1 (36.5, 59.7)	46.9 (33.8, 59.7)	50.5 (40.1, 58.9)	0.25
Race, n (%)				0.15
White	210 (85.4)[b]	178 (86.8)[c]	32 (78.0)	
Nonwhite/other	36 (14.6)	27 (13.2)	9 (22.0)	
Income, n (%)				
<$50,000	58 (23.5)	48 (23.3)	10 (24.4)	0.88
≥$50,000	171 (69.2)	141 (68.4)	30 (73.2)	0.55
Decline to answer	18 (7.3)	17 (8.3)	1 (2.4)	0.19
Education, n (%)				0.38
High school or below	76 (30.8)	61 (29.6)	15 (36.6)	
Above high school	171 (69.2)	145 (70.4)	26 (63.4)	
Marital status, n (%)				0.61
Single/divorced/separated	87 (35.2)	74 (35.9)	13 (31.7)	
Married/common-law	160 (64.8)	132 (64.1)	28 (68.3)	
Ever smoker, n (%)	138 (55.9)	105 (51.0)	33 (80.5)	**0.001**
IBD subtype, n (%)				0.90
Crohn's disease	153 (61.9)	128 (62.1)	25 (61.0)	
Ulcerative colitis	94 (38.1)	78 (37.9)	16 (39.0)	
Active IBD disease, n (%)	99 (41.3)[d]	80 (40.0)[e]	19 (47.5)[f]	0.38
Age of IBD onset, n (%), years				
<17	32 (13)	26 (12.6)	6 (14.6)	0.73
17–40	164 (66.4)	142 (68.9)	22 (53.7)	0.06
>40	51 (20.6)	38 (18.4)	13 (31.7)	0.06
Pain Effects Scale score, median (IQR)	11 (8, 16.3)[b]	11 (7, 16)[e]	15 (9.5, 20)	**<0.0005**
Physical comorbidities, n (%)				
0	73 (29.6)	62 (30.1)	11 (26.8)	0.68
1	58 (23.5)	51 (24.8)	7 (17.1)	0.29
2	45 (18.2)	34 (16.5)	11 (26.8)	0.12
≥3	71 (28.7)	59 (28.6)	12 (29.3)	0.94
Any anxiety disorder, n (%)	72 (29.1)	51 (24.8)	21 (51.2)	**0.001**
By disorder,[g] n (%)				
Panic disorder	12 (4.9)	7 (3.4)	5 (12.2)	**0.02**
Social phobia	32 (13)	22 (10.7)	10 (24.4)	**0.02**
Specific phobia	19 (7.7)	12 (5.8)	7 (17.1)	**0.01**
Generalized anxiety disorder	24 (9.7)	14 (6.8)	10 (24.4)	**0.001**
Agoraphobia	11 (4.5)	7 (3.4)	4 (9.8)	0.07
Obsessive compulsive disorder	12 (4.9)	9 (4.4)	3 (7.3)	0.42
Post-traumatic stress disorder	13 (5.3)	9 (4.4)	4 (9.8)	0.16
Major depressive disorder, n (%)	98 (39.7)	73 (35.4)	25 (61.0)	**0.02**

[a]At baseline visit. [b]n = 246. [c]n = 205. [d]n = 240. [e]n = 200. [f]n = 40. [g]No participants met the criteria for SCID lifetime diagnosis of a general medical condition/substance-induced anxiety disorder. Bold indicates statistically significant findings ($P \leq 0.05$). *P* values generated using χ^2 tests (categorical) and Student *t* tests (continuous).

the general population,[6] those with active IBD may moderate their alcohol consumption to lessen IBD symptom exacerbation. The lifetime prevalences of drug abuse and dependence in those with IBD were similar to estimates in the American general population (abuse, 7.3% vs 7.7%; dependence, 3.6% vs 2.6%).[22]

Rates of nonmedical ever opioid use were low (n = 4, 1.6%). A 2014 study using a population-based Manitoba IBD database reported that within 10 years of IBD diagnosis, 5% were heavy opioid users.[24] However, heavy use does not imply misuse. Possible reasons for the low prevalence of ever opioid use in the current study may be a low transition from medical to nonmedical use or a reluctance to report nonmedical use of prescription opioids.

In persons with IBD, we found that predictors of SUD were similar to those that have been previously established in the general population.[8, 9, 20–21, 25] On multivariable analysis, we found the factor with the strongest association with SUD was smoking history, followed by male sex, lifetime AD, and higher impact of pain. In the general population, smoking and SUD are strongly associated.[25–27] A study of 34,653 Americans found individuals with alcohol abuse or dependence (64.9%) and drug abuse or dependence (75.4%) were more likely to have ever smoked than those with no lifetime psychiatric diagnosis (32.3%).[26] Proposed mechanisms underlying the relation between SUD and smoking include behavioral and neurochemical links among substances and comorbid psychiatric disorders.[25] Nicotine and other substances share neuronal pathways and facilitate the release of common neurotransmitters, including dopamine, norepinephrine, endogenous opioid peptides, and endocannabinoids that reward and reinforce use.[27] Of note, we also found smoking history was associated with SUD even after adjusting for AD and MDD, suggesting comorbid AD and MDD do not fully explain the association between smoking and SUD in those with IBD.

Our finding that male sex was associated with SUD is consistent with predictors of SUD in the general population.[21, 22] Proposed explanations for the higher prevalence of SUD in men include sex differences in brain organization and hormonal systems,[28] higher impulsivity and risk-taking in men,[29] the greater stigmatization of substance use in women,[30] and a greater tendency for women to refrain from activities that are not culturally sanctioned.[28]

Anxiety disorders and MDD are well-established correlates of SUD in the general population.[9] For AD, several factors have been proposed to explain this phenomenon, including self-medication of anxiety, shared vulnerability factors, and the induction of AD by substances' toxic effects.[31–32] Substance use disorder in individuals with comorbid IBD/AD warrants additional clinician attention, as comorbid AD and SUD worsens

TABLE 2. Occurrence of Substance Use in the Study Participants (n = 247)

Any SCID-diagnosed Lifetime SUD, n (%)	41 (16.6)
By disorder, n (%)	
Alcohol abuse	23 (9.3)
Alcohol dependence	18 (7.3)
Drug abuse	18 (7.3)
Drug dependence	9 (3.6)
Ever substance use, n (%)	52 (21.1)
Type, n (%)	
Cannabis	48 (19.4)
Sedatives/hypnotics/anxiolytics	0
Stimulants	4 (1.6)
Opioids	4 (1.6)
Cocaine	7 (2.8)
Hallucinogens/PCP	9 (3.6)
Other	0

Abbreviations: PCP, phencyclidine.

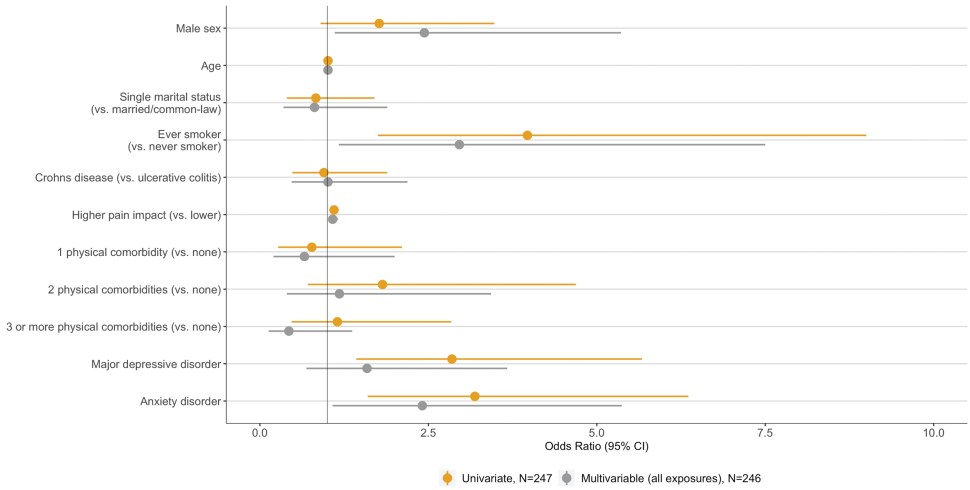

FIGURE 1. Logistic regression analyses for factors associated with substance use disorders (outcome) in those with inflammatory bowel disease. Univariate analyses, n = 247; higher pain impact univariate analysis, n = 246. Multivariable analysis, n = 246. C-statistic = 0.79. Hosmer-Lemeshow Goodness of Fit $\chi^2 = 7.66$, $P = 0.47$. Univariate analyses include each individual variable, and the multivariable analysis includes all listed variables in a single model. This figure visualizes the content of, Supplementary Table 1.

prognosis for both AD and SUD, in general.[34, 35] For MDD and SUD, a systematic review and meta-analysis found a stronger association between MDD and SUD than between AD and SUD in the general population.[9] Unexpectedly, the significant association between lifetime MDD and SUD in IBD was attenuated after adjusting for other factors. Inflammatory bowel disease may moderate the association between depression and SUD, which presents an area for future research.

Consistent with prior research that found pain frequency is associated with an elevated risk of alcohol abuse/dependence and opioid abuse/dependence,[20] we found that elevated impact of pain in those with IBD was significantly associated with the likelihood of having an SUD in both the unadjusted and adjusted analyses. The association between higher pain impact and SUD may be explained by self-medication and the theorized potential for some substances to induce hyperalgesia and thus increase pain impact over time.[20]

This study had many strengths. Diagnoses of AD, MDD, and SUD were established via the SCID, the gold standard for the assessment of mental disorders. Additionally, our study design allowed collection of highly detailed demographic and clinical participant characteristics. Our sample was representative of the IBD population; participants were recruited from both the community and clinics, and participant characteristics in our study were similar to those in other IBD cohorts.[10] We were, however, limited by the cross-sectional nature of our study, which restricted analysis of the influence of IBD clinical factors on SUD over time. Although we had assessments of symptomatic disease activity, we did not have data on the burden of disease over time, rates of surgery, frequency of hospitalization, or IBD-associated disability, which may all affect the prevalence of SUD. Our study did not seek to address rates of treatment and burden of disease of SUD in those with IBD or clinical outcomes of comorbid IBD/SUD, which represent important areas of future investigation. The DSM-5 replaced the DSM-IV after this study was designed. In the DSM-5, substance abuse (diagnosed on meeting ≥1 criterion) and dependence (threshold ≥3 criteria) disorders are combined into a single substance use disorder (≥2 criterion).[36] This change in nosology may affect prevalence of lifetime SUD.

Since the collection of this study's data, Canada legalized the nonmedical use of cannabis for adults.[37] Given the high rate of nonmedical cannabis use in this study, future investigation of ever use of cannabis in the Canadian IBD population, postlegalization, is warranted. In addition, medical cannabis prescribed by a physician has been available in Canada since 2001.[37] We did not discern in this study if nonmedical cannabis users had a history of medical cannabis use. A recent study of 201 persons with IBD found individuals using medical cannabis have characteristics associated with increased vulnerability to substance misuse when compared with those using cannabis recreationally.[38] Persons using cannabis to treat their IBD symptoms were more likely to report using it for coping reasons ($P = 0.016$) and demonstrate higher levels of impulsivity ($P = 0.004$) and depressive symptoms ($P = 0.012$).[38] Further investigations regarding the appropriate use of medical cannabis and a possible correlation to SUD in those with IBD are imperative.

In conclusion, 1 in 6 persons with IBD met the criteria for SUD. Individuals with a history of smoking, higher reported impact of pain, comorbid AD, and males were at elevated risk of SUD and could be targeted for screening of SUD in clinical practice. The substantial individual and societal burden of SUD and the prevalence of undertreatment of SUD in the general population[39] highlight the importance of our findings and the value of subsequent investigation of SUD in those with IBD.

SUPPLEMENTARY DATA

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

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