Cannabis use amongst patients with inflammatory bowel disease

Simon Lal[a,b], Neeraj Prasad[b], Manijeh Ryan[a], Sabrena Tangri[a], Mark S. Silverberg[a], Allan Gordon[a] and Hillary Steinhart[a]

Background **Experimental evidence suggests the endogenous cannabinoid system may protect against colonic inflammation, leading to the possibility that activation of this system may have a therapeutic role in inflammatory bowel disease (IBD). Medicinal use of cannabis for chronic pain and other symptoms has been reported in a number of medical conditions. We aimed to evaluate cannabis use in patients with IBD.**

Methods **One hundred patients with ulcerative colitis (UC) and 191 patients with Crohn's disease (CD) attending a tertiary-care outpatient clinic completed a questionnaire regarding current and previous cannabis use, socioeconomic factors, disease history and medication use, including complimentary alternative medicines. Quality of life was assessed using the short-inflammatory bowel disease questionnaire.**

Results **A comparable proportion of UC and CD patients reported lifetime [48/95 (51%) UC vs. 91/189 (48%) CD] or current [11/95 (12%) UC vs. 30/189 (16%) CD] cannabis use. Of lifetime users, 14/43 (33%) UC and 40/80 (50%) CD patients have used it to relieve IBD-related symptoms, including abdominal pain, diarrhoea and reduced appetite. Patients were more likely to use cannabis for symptom relief if they had a history of abdominal surgery [29/48 (60%) vs. 24/74 (32%); $P=0.002$], chronic analgesic use [29/41 (71%) vs. 25/81 (31%); $P<0.001$], complimentary alternative medicine use [36/66 (55%) vs. 18/56 (32%); $P=0.01$] and a lower short inflammatory bowel disease questionnaire score (45.1 ± 2.1 vs. 50.3 ± 1.5; $P=0.03$). Patients who had used cannabis [60/139 (43%)] were more likely than nonusers [13/133 (10%); $P<0.001$ vs. users] to express an interest in participating in a hypothetical therapeutic trial of cannabis for IBD.**

Conclusion **Cannabis use is common amongst patients with IBD for symptom relief, particularly amongst those with a history of abdominal surgery, chronic abdominal pain and/or a low quality of life index. The therapeutic benefits of cannabinoid derivatives in IBD may warrant further exploration.** *Eur J Gastroenterol Hepatol* **00:000–000** © **2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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[a]The IBD Clinic, Mount Sinai Hospital, Toronto, Ontario, Canada and [b]Intestinal Failure Unit, Salford Royal NHS Foundation Trust, Salford, UK

Correspondence to Simon Lal, MD, PhD, Intestinal Failure Unit, Salford Royal NHS Foundation Trust, Eccles Old Road, Salford, M6 8HD, UK
Tel: +44 161 206 5148; fax: +44 161 206 4690;
e-mail: simon.lal@srft.nhs.uk

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Introduction

The recreational use of *Cannabis sativa* – also known as marijuana – is not uncommon because of its psychoactive properties; in 2008, the Canadian Alcohol and Drug Use Monitoring Survey recorded that 11.4% of the population had used cannabis in the preceding year, with 43.9% reporting use at some point in their lifetime [1]. The medicinal use of cannabis is also well recognized, and patients have used the drug to control symptoms in a number of disorders, such as cancer, [2] multiple sclerosis [3] and HIV infection [4]. Indeed, 1.9% of 2508 adults surveyed in the Canadian province Ontario in 1998 reported using cannabis in the preceding year, with the principal benefit reported for symptoms of pain and/or nausea of varied disease aetiology [5]. A previous study from Spain evaluated drug abuse amongst 214 patients with inflammatory bowel disease (IBD) and found that 10% of patients surveyed admitted to consuming drugs, principally cannabis derivatives [6].

The mechanism by which cannabis may provide therapeutic benefit is unclear. Cannabis contains over 60 cannabinoid compounds, and identification of the main active component, Δ^9-tetrahydrocannabinol, has allowed isolation of two cannabinoid receptors: CB_1 and CB_2 [7]. CB_1 receptors are located throughout the gastrointestinal tract whereas CB_2 receptors are expressed by lamina propria plasma cells and activated macrophages, as well as by myenteric and submucosal plexus ganglia in the ileum; emerging experimental evidence suggests that the endogenous ligands for these receptors ('endocannabinoids') may play a role in modulating a variety of gastrointestinal responses, including motility, secretion and inflammation [8,9]. Indeed, further evidence, principally from animal models, suggests that endocannabinoids may play a role in limiting intestinal inflammation, whereas increased endocannabinoid levels and CB_1 and CB_2 receptor expression have been shown in intestinal biopsy specimens from patients with IBD [8,9]. These data suggest that the

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endocannabinoid system may play a role in the pathophysiology of IBD and, perhaps, that therapeutic modulation of that system may prove to be of benefit to patients.

We aimed to evaluate the use of cannabis in a cohort of patients with IBD and to determine whether patients perceived that they attained symptomatic benefit from using the drug. We also aimed to compare the use of cannabis with other forms of complimentary alternative medicine (CAM).

Methods

Patients and procedure

The study consisted of a cross-sectional survey of 291 patients with IBD attending the Mount Sinai Hospital IBD Centre (Toronto), a tertiary care outpatient clinic, between January and May 2006. All patients were at least 18-years old and their diagnosis of ulcerative colitis (UC) or Crohn's disease (CD) had been confirmed by radiology and/or endoscopy with biopsy using accepted criteria [10]. Patients were asked to complete a questionnaire with regard to demographics, psychosocial factors, disease and therapy history, quality of life and current or previous cannabis use. The questionnaire was anonymised. The study was approved by the Research Ethics Board of Mount Sinai Hospital. All patients provided written, informed consent.

Measures

Demographics and psychosocial characteristics

Sex, age, marital status, ethnicity and employment were assessed through the questionnaire. Alcohol abuse or dependency was assessed using the 'Cut down, Annoyed, Guilty, Eye-opener (CAGE)' score, which is a validated screening instrument designed to assess alcohol dependence or abuse [11]. The total CAGE score ranges from 0 to 4, based on responses to the following four questions: have you ever felt you should cut down your drinking, have people ever annoyed you by criticizing your drinking, have you ever felt bad or guilty about your drinking and have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (an eye opener). In addition, patients were asked about previous or current tobacco smoking and illicit drug use. Psychiatric history was evaluated, particularly any history of depression necessitating medication.

Disease characteristics

Patients were asked about their disease characteristics with a focus on the diagnosis, age at diagnosis, need for hospital admission in the last year, previous abdominal surgery and previous and current therapies. The latter included evaluation of conventional IBD-related medications, as well as the use of complimentary and alternative medicines in the preceding year. Patients were also asked about the prolonged (more than one month) use of analgesics for abdominal pain (excluding use within two months of surgery). Quality of life was assessed using the short inflammatory bowel disease questionnaire (SIBDQ), which contains 10 questions and has been shown to assess the health related quality of life in IBD patients [12].

Cannabis use

Current and/or previous cannabis use was evaluated through a series of questions with regard to frequency, duration, mode (e.g. smoked as joint, ingested) and side-effects. Patients were specifically asked to indicate if they had used cannabis to alleviate IBD-related symptoms. Finally, patients were asked to indicate their interest in participating in a hypothetical therapeutic trial of cannabis for IBD.

Statistics

Statistical analyses were carried out using the SPSS 11.0 Statistical Package for the Social Sciences (SPSS Inc. Chicago, Illinois, USA). Data are expressed as mean ± standard error. Categorical data were compared using Pearson χ^2 analysis; continuous data were analyzed using one-way ANOVA. *P*-values of less than 0.05 were considered statistically significant.

Results

Demographic and psychosocial characteristics

Table 1 outlines the demographic and socioeconomic characteristics of the study population. There were no significant differences in the demographic characteristics, employment status or history of alcohol or noncannabis illicit drug use by UC or CD patients. Of patients reporting a history of depressive illness, most [14/19 (73.7%) UC patients and 15/21 (71.4%) CD patients] stated that the diagnosis of depression had been made following the onset of their IBD.

Disease characteristics

Disease characteristics of the study population are outlined in Table 2. Patients with CD had a younger

Table 1 Demographic and psychosocial characteristics of the study population

	UC ($n=100$)	CD ($n=191$)
Demographic data		
Mean age (SEM)	33.1 (1.2)	33.5 (0.9)
Female (%)	66.0	55.0
Married (%)	44.0	45.5
Ethnicity (%)		
Caucasian	75.0	81.0
Afro-Caribbean	0	3.0
Asian	9.0	3.0
Other	16.0	13.0
Psychosocial data		
Currently employed (%)	72.0	62.0
Mean CAGE score (SEM)	0.32 (0.09)	0.39 (0.07)
Illicit drug use (excluding cannabis) (%)	1.0	1.7
History of depression (%)	19.0	10.7

CAGE, Cut down, Annoyed, Guilty, Eye-opener; SEM, mean ± standard error.

age of onset and reported a greater incidence of previous abdominal surgery, current use of immunosuppressive agents and/or infliximab. CD patients also recorded a higher SIBDQ score compared with UC patients, but there was no difference in recent IBD-related hospitalizations or in the use of analgesics for abdominal pain between the two groups. Similarly, there was no difference in current or previous CAM use by UC or CD patients. Reported CAM use for IBD symptom relief was as follows: 38/100 (38%) UC and 68/188 (36.2%) CD patients used herbal remedies; 11/100 (11%) UC and 21/190 (11.1%) CD patients used acupuncture; 5/100 UC (5%) and 9/190 (4.7%) CD patients used aromatherapy; 1/100 (1%) UC and 4/190 (2.1%) CD patients used hypnotherapy, 26/100 (26%) UC and 51/190 (26.8%) CD patients used naturopathy.

Cannabis use

The demographic and psychosocial characteristics of lifetime cannabis users and nonusers are shown in Table 3. Three-quarters (75%) African Canadians, 3/14 (21.4%) Asians and 121/226 (53.5%) Caucasians reported current or previous cannabis use, but the numbers within former two groups were too small to draw statistical conclusions. Notably, while a history of current or previous cannabis use was higher in alcohol consumers than alcohol abstainers [93/154 (59.1%) vs. 46/129 (35.7%); $P < 0.05$], there was no significant difference in the CAGE score between cannabis users and nonusers. The mean duration of cannabis use (current or previous) was 7 years (range four months to 30 years). Most cannabis users [76/136 (55.9%)] reported doing so once per month or less, although a significant minority [23/136 (16.2%)] reported using cannabis at least daily or several times per day. 77.2% of users smoked cannabis as a joint without tobacco, 17.7% of users smoked it with tobacco, 2.9% used a water pipe, whereas 1% reported oral ingestion.

A comparable proportion of UC and CD patients reported lifetime [48/95 (50.5%) UC vs. 91/189 (48.1%) CD] or current [11/95 (11.6%) UC vs. 30/189 (15.9%) CD] use of cannabis. Of lifetime cannabis users, both UC and CD patients used it to improve stress levels [19/48 (39.6%) UC; 39/88 (44.3%) CD] and sleep [16/48 (33.3%) UC; 31/88 (35.2%) CD]. Notably, 14/43 (32.6%) UC and 40/80 (50.0%) CD patients had used it with good effect to relieve IBD-related symptoms ($P = 0.06$ UC vs. CD), which included abdominal pain [13/14 (92.8%) UC vs. 38/40 (95.0%) CD; $P = 0.5$], diarrhoea [9/14 (64.3%) UC vs. 9/40 (22.5%) CD; $P < 0.05$] and reduced appetite [12/14 (85.7%) UC vs. 28/40 (70.0%) CD; $P = 0.4$]. Patients who used cannabis for IBD symptom relief used it more frequently than those who did not use it for symptom relief (Fig. 1). Furthermore, patients were more likely to use cannabis for symptom relief if they had a history of abdominal surgery, chronic analgesic use, alternative/complimentary medicine use (Fig. 2) and a lower SIBDQ score (45.1 ± 2.1 vs. 50.3 ± 1.5; $P = 0.03$).

Table 2 Disease characteristics and medication use by the study population

	UC ($n=100$)	CD ($n=191$)	Statistical significance
Disease characteristics			
Mean age at diagnosis (SEM)	26.4 (1.2)	22.8 (0.8)	$P<0.05$
IBD-related hospitalization in previous year (% patients)	28.0	36.2	NS
Previous abdominal surgery (%)	23.0	50.5	$P<0.05$
Mean SIBDQ score (SEM)	45.7 (1.3)	49.3 (1.0)	$P<0.05$
Current corticosteroid therapy (%)	25.0	10.5	$P<0.05$
Current azathoprine, 6-mercaptopurine or methotrexate therapy (%)	18.0	37.7	$P<0.05$
Current anti-TNF therapy (%)	8.0	19.4	$P<0.05$
Current/previous analgesics for abdominal pain for more than 1-month (%)	32.0	39.7	NS
Current/previous CAM use (%)	50.0	45.0	NS

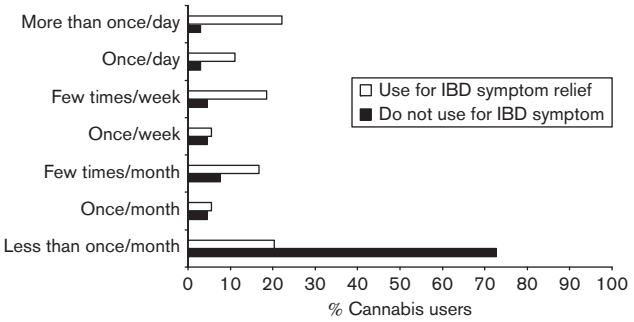
CAM, complimentary alternative medicine; IBD, inflammatory bowel disease; NS, not significant; SEM, mean ± standard error; SIBDQ, short inflammatory bowel disease questionnaire; TNF, tumour necrosis factor.

Table 3 Demographic characteristics of patients by lifetime cannabis use

	Current or previous cannabis use		
	Yes ($n=139$)	No ($n=145$)	Statistical significance
Demographic data			
Mean age (SEM)	31.6 ± 0.9	35.1 ± 1.2	$P<0.05$
Female (%)	51.1	66.2	$P<0.05$
Married (%)	41.3	49.7	NS
Psychosocial data			
Currently employed (%)	71.9	59.7	$P<0.05$
Current or previous smoker (%)	19.4	7.2	$P<0.05$
Mean CAGE score (SEM)	0.41 ± 0.07	0.27 ± 0.08	NS
History of depression (%)	17.4	9.9	NS

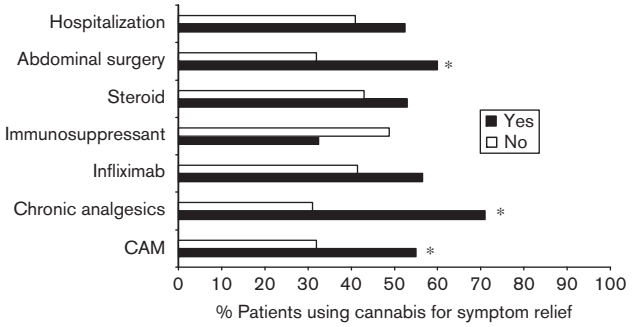
CAGE, Cut down, Annoyed, Guilty, Eye-opener; SEM, mean ± standard error.

Fig. 1



Frequency of cannabis use by patients. Patients who used cannabis for inflammatory bowel disease symptom relief used it more frequently than those who did not use it for symptom relief.

Fig. 2



Percentage of patients using cannabis for symptom relief according to current and/or previous therapies.

The following side-effects were reported by patients, with no difference reported between patients with UC and those with CD: feeling 'high' (easy laughing, heightened awareness: 85.6%); dry mouth (67.7%); drowsiness (68.0%); paranoia (32%); palpitations (30.5%); anxiety (23.5%); memory loss (17.8%); hallucinations (4.2%); depression (1.7%).

Although a comparable proportion of both UC [56/95 (58.9%)] and CD [98/184 (53.3%)] patients stated that they may be interested in participating in a hypothetical therapeutic trial of cannabis for IBD, patients who had used cannabis were more likely than nonusers to express such an interest [60/139 (43%) vs. 13/133 (10%); $P < 0.001$]. No patients in this study had previously used a synthetic cannabinoid for IBD treatment.

Discussion

Current and lifetime use of cannabis reported by patients with UC or CD in this study is comparable to that reported by the general population in the Canadian Alcohol and Drug Use Monitoring Survey of 2008, which found 11.4% had used cannabis in the preceding year, with a lifetime incidence of 43.9% [1]. Current use of cannabis by Canadian patients in this study was also comparable to that found by Garcia-Planella *et al.* [6] for Spanish patients with IBD. Our study also showed that a significant proportion of patients used cannabis to relieve a number of IBD-related symptoms, and that these patients used cannabis more frequently than those who use it solely for recreational purposes. The vast majority of patients using cannabis for their disease did so predominantly to relieve abdominal pain, and, perhaps reflecting this behaviour, patients with a history of abdominal pain, chronic analgesic use and/or those with a lower SIBDQ score, were more likely to use the drug.

The reason why patients perceived symptomatic benefit from using cannabis remains speculative, although patients' perception that use of the drug can lead to improvement in abdominal pain has received mechanistic support from a variety of experimental models which have evidence that activation of both CB_1 and CB_2 receptors can attenuate visceral pain [8,9]. Furthermore, any analgesic property of cannabis may be particularly beneficial in patients with inflammatory disease, as it has been shown in a rodent model, that colonic inflammation enhances the antinociceptive effect of CB_1 and CB_2 receptor activation [13]. Patients with UC, in particular, reported using cannabis to improve diarrhoeal symptoms, and, again, this perceived benefit has received mechanistic support from studies that suggest that cannabinoids inhibit intestinal secretory responses [8,9]; CB_1 receptor activation, for example, has been shown to inhibit cholera toxin-induced diarrhoea in mice [14]. It is equally plausible to speculate that patients perceived benefit from using cannabis to reduce pain and/or diarrhoea because the drug has a direct anti-inflammatory effect on intestinal tissue; indeed, as stated above, experimental evidence suggests that endocannabinoids attenuate intestinal inflammation in animals [8,9], and activation of the CB_2 receptor has been shown to inhibit the release of the proinflammatory cytokine, interleukin 8, from human colonic epithelial cell lines [15]. As in other diseases [16], a significant proportion of both UC and CD patients reported using cannabis to enhance appetite, and the drug's orexigenic properties are well-recognized, with many individuals commonly reporting appetite stimulation or 'the munchies' after use [2].

Forty-seven percent of patients in this study reported using CAM, a figure comparable to those reported in other studies evaluating CAM use in IBD [17–22]. Patients, motives for seeking CAM to manage their symptoms vary: ineffectiveness of conventional therapies, gaining a sense of control over their disease and/or fewer side-effects seem to be amongst the most commonly reported benefits [17–22]. Although, we did not specifically

evaluate why patients chose to use cannabis to manage their symptoms in this study, it is possible that patients may offer similar reasons to those for using CAM; indeed, patients in this study were more likely to use cannabis for symptom relief if they also had a history of CAM use. The risks of cannabis use cannot, of course, be compared with those of other CAM approaches, and it is notable that almost one-third of all patients using cannabis reported significant side-effects such as paranoia and anxiety; indeed, the potential long-term mental health consequences of cannabis are well recognized [23]. A comparable proportion of cannabis-users in this study also reported palpitations, which represent acute effects on the cardiovascular system that are also well recognized [24]. More chronic respiratory consequences, including chronic obstructive pulmonary disease and lung malignancy [25], also remain a concern, particularly as the vast majority of users, including those in this study, smoke the drug. Smoking cannabis, should it contain nicotine, may also prove to be detrimental to patients with CD because of the established adverse effects of smoking nicotine on CD activity, although this may prove to be beneficial to patients with UC, given that nicotine has been shown to have a favourable effect on disease course in UC [26].

Limitations to this study exist. Although patients in this study reported that they perceived symptomatic benefit, clearly our study was not designed to assess disease activity. Patients were attending a tertiary IBD clinic, which may select patients with more severe or complex disease. Furthermore, although the questionnaire was anonymised, it is possible that patients may have still withheld information about their use of cannabis because of fears that it may be passed on; indeed, Garcia-Planella *et al.* [6] found previously that only one-third of patients inform their physician about cannabis use. However, if patients withheld information about cannabis use, then the use of cannabis reported in this study may be an underestimate. Cannabis use remains illegal in most countries, and many oppose any potential plan to legalize its use, not only for recreational purposes, but also for potential medicinal purposes because of concerns over side-effects [27]. Reflecting this concern, a number of synthetic cannabinoid preparations have been developed in recent years for medicinal use, aimed at maximizing therapeutic benefit while minimizing adverse effects. These drugs are becoming licensed for specific uses in Europe and North America – for example Sativex, a mouth spray containing Δ^9-tetrahydrocannabinol together with cannabidiol, was recently granted a license by authorities in the UK for relief of spasticity in patients with multiple sclerosis [28]. Over 50% of both users and nonusers of cannabis in this study expressed an interest in a hypothetical therapeutic trial of cannabis for IBD and our evolving knowledge of the role of the endocannabinoid system in the pathophysiology of gastrointestinal disease, may provide timely impetus to the pharmaceutical development of cannabinoid derivatives as potential anti-inflammatory agents in IBD [8,9].

In summary, our study demonstrates that a significant proportion of patients with IBD use cannabis to relieve IBD-related symptoms, particularly those with a history of abdominal surgery, chronic abdominal pain and/or a low quality of life index. The medicinal use of cannabis is, however, limited by side-effects and as experimental evidence suggests that endocannabinoids may play a role in limiting intestinal inflammation, the development of cannabinoid derivatives with fewer potential side-effects and their use in IBD may warrant further exploration.

Acknowledgement

Conflicts of interest

None declared.

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