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Impact of Cannabis Treatment on the Quality of Life, Weight and Clinical Disease Activity in Inflammatory Bowel Disease Patients: A Pilot Prospective Study

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Key Words

Crohn's disease · Ulcerative colitis · Cannabis · Quality of life, treatment · Weight gain · Disease activity · Inflammatory bowel disease

Abstract

Background and Aims: Inflammatory bowel disease (IBD) patients suffer from significant morbidity and diminished life quality. The plant cannabis is beneficial in various gastrointestinal diseases, stimulating appetite and causing weight gain. Our aims were to assess whether treatment with inhaled cannabis improves quality of life, disease activity and promotes weight gain in these patients. ***Methods:*** Patients with long-standing IBD who were prescribed cannabis treatment were included. Two quality of life questionnaires and disease activity indexes were performed, and patient's body weight was measured before cannabis initiation and after 3 months' treatment. ***Results:*** Thirteen patients were included. After 3 months' treatment, patients reported improvement in general health perception ($p = 0.001$), social functioning ($p = 0.0002$), ability to work ($p = 0.0005$), physical pain ($p = 0.004$) and depression ($p = 0.007$). A schematic scale of health perception showed an improved score from 4.1 ± 1.43 to 7 ± 1.42 ($p = 0.0002$). Patients had a weight gain of 4.3 ± 2 kg during treatment (range 2–8; $p = 0.0002$) and an average rise in BMI of 1.4 ± 0.61 (range 0.8–2.7; $p = 0.002$). The average Harvey-Bradshaw index was reduced from 11.36 ± 3.17 to 5.72 ± 2.68 ($p = 0.001$). ***Conclusions:*** Three months' treatment with inhaled cannabis improves quality of life measurements, disease activity index, and causes weight gain and rise in BMI in long-standing IBD patients.

Introduction

Crohn's disease (CD) is a chronic inflammatory disorder that may affect the gastrointestinal tract from the mouth to the anus. Inflammation is transmural and might therefore be complicated by fistula and abscess formation, perforations and fibrotic strictures. Ulcerative colitis (UC) is a form of inflammatory bowel disease (IBD) which affects mainly the colon, thus causing abdominal pain, bloody diarrhea and weight loss. Both diseases may cause significant morbidity and diminished life quality [1–6]. Treatment options include a variety of anti-inflammatory and immunosuppressant agents. Most commonly used are the 5-ASA anti-inflammatory drugs, corticosteroids, thiopurine drugs (azathioprine

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and 6-mercaptopurine), methotrexate and anti-TNFα agents. Most of these treatments, however, carry a considerable risk for severe side effects [7–12].

The beneficial effect of cannabinoids on the gastrointestinal tract has been recognized for centuries. The plant *Cannabis sativa* is the source of more than 60 aromatic hydrocarbon compounds called cannabinoids, of which delta 9-tetrahydrocannabinol is the main psychotropic constituent. This agent acts via at least two types of cannabinoid receptors, named CB1 and CB2 receptors [13]. CB1 receptors are located mainly on central and peripheral neurons, and in the gastrointestinal tract in the enteric nervous system. By these receptors the cannabinoids cause inhibition of the gastrointestinal motility, mainly by inhibiting ongoing contractile transmitter release [14–16]. The CB2 receptors are located mainly on immune cells [17], but also on some afferent (sensory) nerve terminals [18]. The effect of cannabinoids on the immune system is complex, and mediated through CB1 and CB2 receptors [19]. Both receptors are expressed on B cells, NK cells and mast cells [20, 21]. Cannabinoids suppress Th1 cytokine production and increase Th2 cytokine production, primary via CB2 receptors [22, 23]. Secretion of TNFα is directly inhibited by cannabinoids [21, 24].

The use of cannabis is also known to stimulate appetite and cause weight gain [25, 26]. Recent studies show involvement of the plant in the regulation of appetite, food intake and energy metabolism [27–30].

Thus, treatment with cannabis may have a beneficial effect in patients with IBD who suffer from alerted bowel movements, abdominal pain and loss of appetite. However, despite the fact that sporadic patients self-administer cannabis, investigational data in the literature is scarce. In Israel, inhaled cannabis has been legally registered for palliative treatment of both CD and UC. In this preliminary prospective study, we tried to assess whether treatment with inhaled cannabis improves the quality of life, reduces disease activity and promotes weight gain in patients with IBD.

Patients and Methods

Study Design

The study was an open-label, prospective, single-arm trial.

Study Population

To be included in the study, patients had to have an established diagnosis of CD, UC or colonic IBD unclassified according to accepted clinical-radiological and histopathological criteria, for at least 12 months prior to study entry. Patients were eligible for inclusion if they were prescribed cannabis treatment by their gastroenterologist independently of the present study. Since there are no guidelines for cannabis treatment in the literature, and cannabis is generally reserved for treatment-failing patients, the entire cohort consisted of patients with long-standing diseases who were refractory to most conventional therapies (see Results). Patients' concomitant medications were stable at least 16 weeks prior to inclusion.

Procedures

After signing an informed consent form, patients were asked to fill two standard quality of life questionnaire (EQ-5D and SF-36v2), and their body weight was measured before the initiation of cannabis. After 3 months of treatment, patients filled the same questionnaires again, and their body weight was reassessed. For patients with CD, the Harvey-Bradshaw index for disease activity assessment was performed before treatment initiation and 3 months thereafter. For patients with UC, the partial Mayo score index for disease activity assessment was performed before treatment initiation and 3 months thereafter.

Inhaled cannabis was given by a legally authorized organization, supervised by the Israeli Ministry of Health, which grows the cannabis plants and provides it to patients as prepared cigarettes in the dose of 50 g dry processed plant per month on a compassionate basis free of charge. Patients were instructed to use inhaled cannabis whenever they felt pain. They were guided to take up to 3 inhalations from the prepared cigarettes each time, in order to avoid psychiatric side effects. Since the treatment included plants from various gardening nurseries, there was no standardization for the amount of active materials in the prepared cigarettes.

The study was approved by the Sheba Medical Center ethics committee.

SF-36 Health Survey

The SF-36 health survey is a widely used health status questionnaire constructed to assess health status in medical outcomes studies. The survey is designed to assess eight health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, vitality and general health perception. Results of each of these concepts are shown separately in the results.

EQ-5D Health Survey

The EQ-5D health survey consist of 5 simple questions regarding patient's mobility, self care ability, daily activities, pain and depression and a schematic scale of patients perception of his/her current health status ranging from 0 to 10.

Harvey-Bradshaw Index

The Harvey-Bradshaw index is a simplified questionnaire designed for assessment of Crohn's disease activity, and consists of 5 clinical parameters [31].

Partial Mayo Score

The partial Mayo score is a 9-point scale that includes clinical parameters and excludes the endoscopic appearance of the mucosa [32].

Table 1. Patient and disease characteristics

	Crohn's disease	Ulcerative colitis
Gender (M/F)	8/3	1/1
Mean age, years	44 ± 10.7	29.5 ± 2.1
(range)	(28–62)	(28–31)
Mean disease duration, years	18.2 ± 8.9	14 ± 24
(range)	(5–35)	(11–17)
Disease location		
Terminal ileum (L1)	5	2 patients
Colon (L2)	2	with left
Ileocolon (L3)	4	colitis
Disease behavior		
Nonstricturing nonpenetrating (B1)		
Stricturing (B2)	3	
Penetrating (B3)	8	
Previous intestinal resections, n	6	
Previous operations without bowel resections (including fistula drainage)	5	
Previous medical treatment		
5 ASA	11	2
Immunomodulators	11	2
Corticosteroids	11	2
Anti-TNFα	8	1
Previous TPN treatment	3	
Small bowel obstruction in the past	7	
Concomitant medications		
5 ASA	0	2
Immunomodulators	6	1
Corticosteroids	2	0
Anti-TNFα	5	1
Extraintestinal manifestations	7	1
Smoking status		
Smoker	5	2
Ex smoker	1	0
Never smoked	5	0

Statistical Analysis

The Wilcoxon rank test was employed to evaluate the changes in paired variables in the study group before and after 3 months of cannabis treatment. Correlations were tested by Spearman correlation test. All statistics were performed using MedCalc software (Mariakerke, Belgium). $p < 0.05$ was considered significant.

Results

Study Population

A total of 13 patients were included in the study (4 women and 9 men). Eleven patients suffered from CD, and 2 from UC. Demographic data of the patients and disease characteristics are shown in table 1. In all patients, IBD medications were stable during the 3-month period of the study. All patients used the entire amount of inhaled cannabis supplied each month. No adverse events were reported. None of the patients reported cannabis usage prior to the study.

Assessment of Patients' Quality of Life, SF-36 Health Survey and Physical Aspects of Health

Limitations due to Physical Health Problems. In 12 of 14 daily activities assessed, there was a statistically significant improvement after treatment (p values between 0.0005 and 0.03).

Bodily Pain. Pain severity during the preceding 4 weeks before cannabis initiation was noted as severe or very severe by 10 patients, and was moderate in the other 3. After 3 months of treatment, only 1 patient had very severe pain, 4 had severe pain and the rest had mild to moderate pain ($p = 0.0002$).

Psychological Aspects of Health

General Health Perception. Twelve of 13 patients assessed their health status as bad or not so good before treatment, with a statistically significant change to good and very good in 10 patients, and not so good in the 3 remaining patients after 3 months of treatment ($p = 0.0005$). In a further item of the questionnaire, a similar statistically significant change to a better health status compared to the prior year was noted ($p = 0.001$).

Role Limitations due to Emotional Problems. There was a statistically significant improvement in patients' ability to work after treatment ($p = 0.0005$).

Social Functioning. A statistically significant improvement in patients' ability to maintain social activities was evident after treatment ($p = 0.0002$).

Emotional Stress. There was a statistically significant improvement in emotional stress after treatment (p between 0.001 and 0.0002 for the different items of this section of the questionnaire).

The numerical results of the questionnaire are shown in table 2.

EQ-5D Health Survey

As shown in table 3, there was a significant improvement in 3 of 6 items on this questionnaire. No change was noted in the mobility and self-care ability scores, but they were scored as good even before the treatment.

Harvey-Bradshaw Index

In 11 patients with CD, the Harvey-Bradshaw index was performed in order to clinically assess the utility of

Table 2. Results of the SF-36v2 health survey

	Before treatment	After treatment	p value
General health	4.38 ± 0.65	2.92 ± 0.76	0.0005
General health today compared to 1 year ago	3.77 ± 0.92	2.07 ± 1.18	0.001
Restrictions in daily activities	2.01 ± 0.73	2.61 ± 0.59	<0.0001
Limitations in daily activities due to physical condition	1.86 ± 0.71	3.48 ± 0.78	<0.0001
Limitations in daily activities due to emotional problems	2.52 ± 0.97	3.86 ± 0.86	<0.0001
Restrictions in social life	3.92 ± 0.86	2.3 ± 0.94	0.0002
Physical pain	4.84 ± 0.55	3 ± 1.03	0.0002
Limitations in working ability following pain	4.15 ± 0.55	2.23 ± 0.92	0.0002
General well-being	3.05 ± 0.99	3.17 ± 0.93	0.4758
Frequency of restrictions in social life	2.07 ± 0.76	3.69 ± 0.75	0.002
Self-perception of health condition	3.51 ± 1.39	3.26 ± 1.19	0.0797

Table 3. Results of the EQ-5D health survey

	Before treatment	After treatment	p value
Mobility	1.53 ± 0.66	1.3 ± 0.48	0.9
Self-care ability	1.15 ± 0.55	1.05 ± 0.277	0.9
Daily activities	1.92 ± 0.64	1.53 ± 0.51	0.06
Pain	2.46 ± 0.66	1.76 ± 0.43	0.004
Depression	1.84 ± 0.68	1.23 ± 0.43	0.007
Schematic scale	4.1 ± 1.43	7 ± 1.42	0.0002

Table 4. Results of the Harvey-Bradshaw index

	Before treatment	After treatment	p value
General well-being	2.63 ± 0.67	0.81 ± 0.87	0.0010
Abdominal pain	2.36 ± 0.92	1.09 ± 0.7	0.0039
Number of liquid stools/day	5.27 ± 2.93	3 ± 1.73	0.0039
Abdominal mass	0.27 ± 0.9	0.18 ± 0.6	0.7
Complications	0.63 ± 0.5	0.63 ± 0.5	1

treatment on disease activity. Results are shown in table 4. The initial average score was 11.36 ± 3.17. After 3 months' treatment, the score was reduced to 5.72 ± 2.68 ($p = 0.001$). The main improvement was seen in the parameters of general well-being and abdominal pain. However, there was a considerable reduction in the number of liquid stools per day as well (from an average of 5.54 ± 2.5 per day to an average of 3.18 ± 1.47/day, $p = 0.002$).

Partial Mayo Score

The partial Mayo score was performed in the 2 UC patients that were included in the study. There was a slight decrease in both patients' scores after 3 months' treatment from 6 to 5 points, but the small number of patients with UC precluded statistical analysis.

Weight Change

Before treatment, the patients' average weight was 64.23 ± 10.67 kg (range 48–80), and the average BMI was 20.79 ± 2.9 (range 16.2–24.1). Though the average BMI was within normal limits (between 18.5 and 24.9), 2 patients were severely underweight with BMI values of 16.2 and 17.9. Another 3 patients had BMIs of 19. After 3 months' treatment, the average weight was 68.53 ± 11.36 kg (range 51–88), and the average BMI was 22.4 ± 2.4 (range 17.9–25.7). The 2 patients with the low BMI raised it to 17.9 and 19.1, respectively. Thus, only one of them remained under the normal limits. Therefore, there was an average weight gain of 4.3 ± 2 kg (range 2–8) during treatment ($p = 0.0002$). The average rise in BMI was 1.4 ± 0.61 (range 0.8–2.7; $p = 0.002$). These results are shown graphically in figure 1.

Reduction in Inflammatory Markers

Since our study was not designed to assess the direct effect of cannabis on inflammation, data on inflammatory markers was only available for 6 patients – all of them CD patients.

Table 5. Changes in CRP levels in 6 patients (normal values >0.5)

Before treatment	During treatment
1.6	>0.5
>0.5	>0.5
1.3	>0.5
0.9	>0.5
1.6	>0.5
1.4	>0.5

Results are shown in table 5. Before treatment, 5 patients had elevated CRP levels – between 2- and 3-fold increase from the upper normal range. The average was 1.21 ± 0.4 (normal range <0.5). During treatment, the CRP levels returned to normal range within 40.2 ± 20 days in an average. The sixth patient had normal CRP levels before and after the treatment.

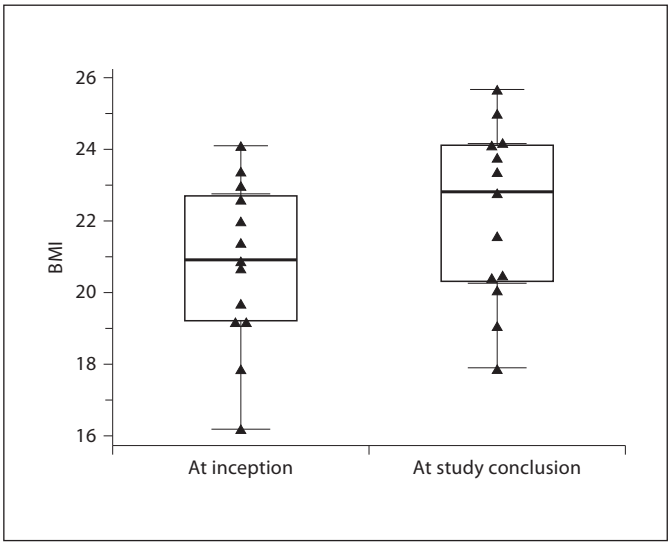

Fig. 1. BMI at study inception and after 3 months of treatment.

Discussion

For centuries, the plant *Cannabis sativa* has been known to be beneficial in various diseases, including diseases involving the gastrointestinal tract. To the best of our knowledge, there are no data in the medical literature addressing its use in IBD patients. In the present preliminary prospective study, we have found that treatment with inhaled cannabis improves quality of life in patients with long-standing CD and UC. Treatment was also shown to cause a statistically significant rise in patients' weight after 3 months of treatment, and improvement in clinical disease activity index in patients with CD. Since there were only 2 patients with UC in the study, the issue of disease activity in these patients needs further evaluation. However, both patients showed mild improvement in the partial Mayo score.

Moreover, the data demonstrated a statistically significant improvement in almost all aspects of patients' daily life. After 3 months' treatment with inhaled cannabis, patients stated an improvement in their health status, their ability to perform daily activities and their ability to maintain social life. Patients reported a statistically significant physical pain reduction during treatment, as well as improvement in mental distress.

Our results can be explained by existing data regarding the effect of cannabinoids on the GI tract. Cumulative data suggests that endocannabinoids have a role in various important physiological and pathophysiological functions in the GI tract. The relevance of these effects to IBD patients could be speculated to stem from its effect on GI motility, on the immune system and its potent action as analgesics. Regarding motility, cannabinoid receptor agonists were shown to inhibit small bowel peristalsis both in vitro [33, 34] and in vivo [15, 16, 35] in animal models. This effect was produced by activating CB1 receptor of rodents.

Cannabinoids were also shown to delay gastric empting in rodents [35], and to reduce both contractile activity of stomach and duodenum and intragastric pressure [35, 36]. Another action of the cannabinoids is inhibition of gastric acid secretion [37]. This effect was shown also in 90 heavy cannabis smokers [38]. These inhibitory effects on GI tract motility and secretion may be beneficial in patients with diarrhea. Indeed, some anecdotal reports suggest effective use of cannabis against dysentery and cholera [39]. In the inflamed gut, both CB1 and CB2 receptor activation may reduce inflammation-associated hypermotility. In a mice model of ileitis, cannabinoid agonists were proven effective in reducing intestinal motility compared to control sham-treated mice [40]. Activation of CB2 receptors also inhibits both the accelerated intestinal motility [41] and the extent of inflammation [42] in experimental bowel inflammation. This inhibitory effect on bowel motility may explain the reduction in the number of liquid stools per day reported by our CD patients.

Cannabinoids are potent analgesics, mainly affecting chronic neuropathic and inflammatory pain [43, 44]. Visceral sensory nerves of the gut are inhibited by CB1 and CB2 receptor selective agonists [45, 46]. CB2 receptor agonists normalize sensory hypersensitivity caused by colon distension in experimental colitis [45]. This effect can explain the significant pain relief expressed by our patients.

In addition to their effects as anti-motility and analgesic agents, cannabinoids may exert a direct inhibitory effect on the immune system, via both CB1 and CB2 receptors [19]. In the gastrointestinal tract, cannabinoid receptors are found on gut-associated lymphoid tissue [47, 48]. Both receptors are expressed on B cells, NK cells and mast cells [20, 21]. Cannabinoids suppress cell-mediated immunity and TH1 cytokine production, and enhance adaptive immunity and TH2 cytokine production [20, 22, 23, 49]. Cannabinoids inhibit LPS-evoked macrophage activation [50], suppress activated macrophages and mast cells [51–53] and were also shown to abrogate TNFα secretion [51]. The anti-inflammatory effect of cannabis use could also be related to the improvement in the clinical index of our CD patients.

Our results showed a significant weight gain of 4.3 ± 2 kg on average after 3 months' treatment with inhaled cannabis. The BMI rose, respectively, by 1.4 ± 0.61. In the current study of the 2 patients with severe underweight, one rose above the bottom limit of BMI 18.5 following treatment, and the other raised her weight from 48 to 53 kg (BMI rose from 16.2 to 17.9). The weight gain observed in our study may be at least partly explained by data pertaining to the effects of endocannabinoids on appetite. Thus, enhanced appetite was evident after stimulation of CB_1 receptors in hypothalamic areas involved in the control of food intake, such as the ventromedial hypothalamus (VMH) [54]. In animal models, the injection of anandamide (endogenous cannabinoid) in the VMH of pre-satiated rats induces hyperphagia. This effect was prevented by previous hypothalamic administration of the selective CB_1 cannabinoid antagonist rimonabant [55].

A recent case series of 30 patients treated with cannabis for severe pain unresponsive to other drugs showed significant pain relief in 28 (93%) of patients [56]. Side effects which included increased appetite were shown in 18 patients. A sense of well-being was reported in 12 patients and weight gain in 7. These results are in agreement with our results showing a significant improvement in quality of life and weight gain in treated patients.

None of our patients complained of any side effect that disturbed their working ability. In fact, as was shown in the results, there was a statistically significant improvement in patients' ability to work after treatment. However, our patient group included students, one pensioner, three businessmen and a film editor – professions that do not require motor coordination. The issue of treatment side effects and restrictions on treatment timing needs further evaluation.

There are several limitations to our study. The design focused on assessment of quality of life changes, weight gain and clinical disease activity in IBD patients and did not address the possible direct effect of cannabis on gut inflammation and mucosal changes. Although some patients did show a reduction in inflammatory markers such as CRP and ESR (see 'Results'), our data are incomplete. We believe this issue merits evaluation by specifically designed studies. Another drawback of our study is a possible selection bias and placebo response. Since we had no control group, the placebo effect was not ruled out. Selection bias might have been caused as a consequence of the study design. In addition, due to the nature of the treatment, we could not assess any dose effect – since quantifications are not relevant in this case. Nevertheless, improved quality of life is one of the main goals in medical treatment, and is often what interests patients the most. Thus, we think the present results are important in demonstrating for the first time that cannabis treatment indeed results in measurable improvement in quality of life of IBD patients. Another drawback is the small number of patients enrolled, and the fact that the study was an observational rather than a blinded controlled trial. Thus, more studies are pertinent in order to validate the results of the present pilot study.

In conclusion, in this preliminary prospective study we found a statistically significant improvement in quality of life measurements and a mean weight gain of 4.3 kg and rise in BMI of 1.4 in long-standing IBD patients, and improvement in the Harvey-Bradshaw index in 11 patients with long-standing CD treated with inhaled cannabis for 3 months. Additional studies are called for in order to assess the direct effect cannabis has on the inflammatory process and mucosal changes in these patients.

References

1 Love JR, Irvine EJ, Fedorak RN: Quality of life in IBD. J Clin Gastroenterol 1992;14:15–19.
2 Casellas F, Arenas JI, Baudet JS, et al: Impairment of health-related quality of life in patients with inflammatory bowel disease: a Spanish multicenter study. Inflamm Bowel Dis 2005;11:488–496.
3 Rubin GP, Hungin AP, Chinn DJ, et al: Quality of life in patients with established inflammatory bowel disease: a UK general practice survey. Aliment Pharmacol Ther 2004;19:529–535.
4 Casellas F, López-Vivancos J, Badia X, et al: Influence of inflammatory bowel disease on different dimensions of quality of life. Eur J Gastroenterol Hepatol 2001;13:567–572.
5 Canavan C, Abrams KR, Hawthorne B, et al: Long-term prognosis in Crohn's disease: factors that affect quality of life. Aliment Pharmacol Ther 2006;23:377–385.
6 Hjortswang H, Järnerot G, Curman B, et al: The influence of demographic and disease-related factors on health-related quality of life in patients with ulcerative colitis. Eur J Gastroenterol Hepatol 2003;15:1011–1020.
7 Gearry RB, Barclay ML, Burt MJ, et al: Thiopurine drug adverse effects in a population of New Zealand patients with inflammatory bowel disease. Pharmacoepidemiol Drug Saf 2004;13:563–567.
8 Fraser AG, Orchard TR, Jewell DP: The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30-year review. Gut 2002;50:485–489.
9 Colombel JF, Loftus EV Jr, Tremaine WJ, et al: The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. Gastroenterology 2004;126:19–31.
10 Schnitzler F, Fidder H, Ferrante M, et al: Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. Gut 2009;58:492–500.
11 Sandborn WJ, Loftus EV: Balancing the risks and benefits of infliximab in the treatment of inflammatory bowel disease. Gut 2004;53:780–782.
12 Lichtenstein GR, Feagan BG, Cohen RD, et al: Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. Clin Gastroenterol Hepatol 2006;4:621–630.
13 Pertwee RG: Pharmacology of cannabinoid CB1 and CB2 receptors. Pharmacol Ther 1997;74:129–180.
14 Shook JE, Burks TF: Psychoactive cannabinoids reduce gastrointestinal propulsion and motility in rodents. J Pharmacol Exp Ther 1989;249:444–449.
15 Izzo AA, Mascolo N, Pinto L, et al: The role of cannabinoid receptors in intestinal motility, defaecation and diarrhoea in rats. Eur J Pharmacol 1999;384:37–42.
16 Landi M, Croci T, Rinaldi-Carmona M, et al: Modulation of gastric emptying and gastrointestinal transit in rats through intestinal cannabinoid CB(1) receptors. Eur J Pharmacol 2002;450:77–83.
17 Hornby PJ, Prouty SM: Involvement of cannabinoid receptors in gut motility and visceral perception. Br J Pharmacol 2004;141:1335–1345.
18 Stander S, Schmelz M, Metze D, Luger T, Rukwied R: Distribution of cannabinoid receptor 1 (CB1) and 2 (CB2) on sensory nerve fibers and adnexal structures in human skin. J Dermatol Sci 2005;38:177–188.
19 Klein TW: Cannabinoid-based drugs as anti-inflammatory therapeutics. Nat Rev Immunol 2005;5:400–411.
20 Klein TW, Newton C, Larsen K: The cannabinoid system and immune modulation. J Leukoc Biol 2003;74:486–496.
21 Samson MT, Small-Howard A, Shimoda LM, et al: Differential roles of CB1 and CB2 cannabinoid receptors in mast cells. J Immunol 2003;170:4953–4962.
22 Yuan M, Kiertscher SM, Cheng Q, et al: Delta 9-tetrahydrocannabinol regulates Th1/Th2 cytokine balance in activated human T cells. J Neuroimmunol 2002;133:124–131.
23 Klein TW, Newton C, Larsen K, et al: Cannabinoid receptors and T helper cells. J Neuroimmunol 2004;147:91–94.
24 Facchinetti F, Del Giudice E, Furegato S, et al: Cannabinoids ablate release of TNFalpha in rat microglial cells stimulated with lipopolysaccharide. Glia 2003;41:161–168.
25 Abel EL: Cannabis: effects on hunger and thirst. Behav Biol 1975;15:255–281.
26 Berry EM, Mechoulam R: Tetrahydrocannabinol and endocannabinoids in feeding and appetite. Pharmacol Ther 2002;95:185–190.
27 Di Marzo V, Matias I: Endocannabinoid control of food intake and energy balance. Nat Neurosci 2005;8:585–589.
28 Kirkham TC: Endocannabinoids in the regulation of appetite and body weight. Behav Pharmacol 2005;16:297–313.
29 Sharkey KA, Pittman QJ: Central and peripheral signaling mechanisms involved in endocannabinoid regulation of feeding: a perspective on the munchies. Sci STKE 2005;277:15.
30 Pagotto U, Marsicano G, Cota D, et al: The emerging role of the endocannabinoid system in endocrine regulation and energy balance. Endocr Rev 2006;27:73–100.
31 Harvey R, Bradshaw J: A simple index of Crohn's disease activity. Lancet 1980;i:514.
32 Lewis JD, Chuai S, Nessel L, et al: Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. Inflamm Bowel Dis 2008;14:1660–1666.
33 Izzo AA ,Mascolo N, Tonini M, et al: Modulation of peristalsis by cannabinoid CB_1 ligands in the isolated guinea pig ileum. Br J Pharmacol 2000;129:984–990.
34 Heinemann A, Shahbazian A, Holzer P: Cannabinoid inhibition of guinea pig intestinal peristalsis via inhibition of excitatory and activation of inhibitory neural pathways. Neuropharmacology 1999;38:1289–1297.
35 Shook JE, Burks TF: Psychoactive cannabinoids reduce gastrointestinal propulsion and motility in rodents. J Pharmacol Exp Ther 1989;249:444–449.
36 Krowicki ZK, Moerschbaecher JM, Winsauer PJ, et al: Δ^9-tetrahydrocannabinol inhibits gastric motility in the rat through cannabinoid CB_1 receptors. Eur J Pharmacol 1999;371:187–196.
37 Coruzzi G, Adami M, Coppelli G, et al: Inhibitory effect of the cannabinoid receptor agonist WIN 55,212–2 on pentagastrin-induced gastric acid secretion in the anaesthetized rat. Naunyn Schmiedebergs Arch Pharmacol 1999;360:715–718.
38 Nalin DR, Rhead J, Rennels M, et al: Cannabis, hypochlorhydria and cholera. Lancet 1978;ii:859–862.
39 Mechoulam R: The pharmacohistory of Cannabis sativa; in Mechoulam R (ed): Cannabinoids as Therapeutic Agents. Boca Raton, CRC Press, 1986, pp 1–19.
40 Izzo AA, Fezza F, Capasso R, et al: Cannabinoid CB1-receptor mediated regulation of gastrointestinal motility in mice in a model of intestinal inflammation. Br J Pharmacol 2001;134:563–570.
41 Mathison R, Ho W, Pittman QJ, et al: Effects of cannabinoid receptor-2 activation on accelerated gastrointestinal transit in lipopolysaccharide-treated rats. Br J Pharmacol 2004;142:1247–1254.
42 Kimball ES, Schneider CR, Wallace NH, et al: Agonists of cannabinoid receptor 1 and 2 inhibit experimental colitis induced by oil of mustard and by dextran sulfate sodium. Am J Physiol Gastrointest Liver Physiol 2006;291:G364–G371.
43 Richardson JD, Aanonsen L, Hargreaves KM: Antihyperalgesic effects of spinal cannabinoids. Eur J Pharmacol 1998;345:145–153.
44 Siegling A, Hofmann HA, Denzer D, et al: Cannabinoid CB(1) receptor upregulation in a rat model of chronic neuropathic pain. Eur J Pharmacol 2001;415:R5–R7.
45 Sanson M, Bueno L, Fioramonti J: Involvement of cannabinoid receptors in inflammatory hypersensitivity to colonic distension in rats. Neurogastroenterol Motil 2006;18:949–956.
46 Hillsley K, McCaul C, Aerssens J, et al: Activation of the cannabinoid 2 (CB2) receptor inhibits murine mesenteric afferent nerve activity. Neurogastroenterol Motil 2007;19:769–777.

47 Lynn AB, Herkenham M: Localization of cannabinoid receptors and nonsaturable high-density cannabinoid binding sites in peripheral tissues of the rat: implications for receptor-mediated immune modulation by cannabinoids. J Pharmacol Exp Ther 1994; 268:1612–1623.
48 Kulkarni-Narla A, Brown DR: Localization of CB1-cannabinoid receptor immunoreactivity in the porcine enteric nervous system. Cell Tissue Res 2000;302:73–80.
49 Roth MD, Baldwin GC, Tashkin DP: Effects of delta-9-tetrahydrocannabinol on human immune function and host defense. Chem Phys Lipids 2002;121:229–239.
50 Chang YH, Lee ST, Lin WW: Effects of cannabinoids on LPS-stimulated inflammatory mediator release from macrophages: involvement of eicosanoids. J Cell Biochem 2001;81:715–723.
51 Facchinetti F, Del Giudice E, Furegato S, et al: Cannabinoids ablate release of TNFalpha in rat microglial cells stimulated with lipopolysaccharide. Glia 2003;41:161–168.
52 Small-Howard AL, Shimoda LM, Adra CN, et al: Anti-inflammatory potential of CB1-mediated cAMP elevation in mast cells. Biochem J 2005;388:465–473.
53 Vannacci A, Passani MB, Pierpaoli S, et al: Nitric oxide modulates the inhibitory effect of cannabinoids on the immunological activation of guinea pig mast cells. Inflamm Res 2003;52(suppl 1):S7–S8.
54 Pacher P, Batkai S, Kunos G: The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev 2006;58: 389–462.
55 Jamshidi N, Taylor DA: Anandamide administration into the ventromedial hypothalamus stimulates appetite in rats. Br J Pharmacol 2001;134:1151–1154.
56 Lynch ME, Young J, Clark AJ: A case series of patients using medicinal marihuana for management of chronic pain under the Canadian Marihuana Medical Access Regulations. J Pain Symptom Manage 2006;32:497–501.