To: ACIA
From: Loretta
Re: IBS & Cannabis

Medical Marijuana Uses: Cannabis Calms IBS

Posted by Marijuana Doctors on 09/15/2011 in Medical Marijuana Conditions

There's some good news for patients suffering from Irritable Bowel Syndrome. Cannabis was recently proven to decrease colonic motility in patients with irritable bowel syndrome (IBS), according to a study called *"*Pharmacogenetic Trial of a Cannabinoid Agonist Shows Reduced Fasting Colonic Motility in Patients with Non-Constipated Irritable Bowel Syndrome*."*

For those unfamiliar with IBS, it is a disorder that leads to abdominal pain and cramping, changes in bowel movements, and other symptoms. About 1 in 6 people in the U.S. have symptoms of IBS. It is the most common intestinal problem that causes patients to see a gastroenterologist. A recent survey from the *European Journal of Gastroenterology and Hepatology* shows that it's very common for patients with IBS regularly use medical marijuana to alleviate their symptoms. Now this new study confirms cannabis' benefits for IBS patients.

This new cannabis/IBS study, which is published in the journal *Gastroenterology*, found that the administration of synthetic THC (aka dronabinol) is beneficial for those suffering with IBS. Researchers at the Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER) in Rochester, Minnesota studied 75 individuals with IBS—35 with IBS with constipation, 35 with IBS with diarrhea, and with 5 IBS alternating). Each test subject was randomly assigned to groups that were given 1 dose of placebo or 2.5 mg or 5.0 mg dronabinol. All participants given the synthetic THC showed decreased colonic motility, which is the contraction of intestinal muscles and movement of its contents. The most significant results in IBS patients with diarrhea and in subjects with alternating diarrhea and constipation.

Researchers concluded that **"In patients with IBS with diarrhea or alternating, dronabinol reduces fasting colonic motility."** Dronabinol is presently a schedule III controlled substance that is currently is approved by the US Food and Drug Administration for the treatment of severe nausea and cachexia (wasting syndrome).

But we may soon see the drub being approved for IBS thanks to the results of this new study

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Pharmacogenetic Trial of a Cannabinoid Agonist Shows Reduced Fasting Colonic Motility in Patients with Non-Constipated Irritable Bowel Syndrome

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Abstract

Background

Cannabinoid receptors are located on cholinergic neurons. Genetic variants that affect endocannabinoid metabolism are associated with colonic transit in patients with irritable bowel syndrome with diarrhea (IBS-D). We compared the effects of dronabinol, a non-selective agonist of the cannabinoid receptor, with those of placebo on colonic motility and sensation in patients with IBS, and examined the effects of IBS subtype and specific genetic variants in cannabinoid mechanisms.

Methods

Seventy-five individuals with IBS (35 with IBS with constipation [IBS-C], 35 with IBS-D, and with 5 IBS-alternating [IBS-A]) were randomly assigned to groups that were given 1 dose of placebo or 2.5 mg or 5.0 mg dronabinol. We assessed left colonic compliance, the motility index (MI), tone, and sensation, during fasting and after a meal. We analyzed the single nucleotide polymorphisms *CNR1 rs806378*, *FAAH rs324420*, and *MGLL rs11538700*.

Results

In all patients, dronabinol decreased fasting proximal left colonic MI, compared with placebo (overall *P*=.05; for 5 mg dronabinol, *P*=.046), decreased fasting distal left colonic MI (overall *P*=.08; for 5 mg, *P*=.13), and increased colonic compliance (*P*=.058). The effects of dronabinol

were greatest in patients with IBS-D or -A (proximal colonic MI, overall *P*=.022; compliance, overall, *P*=.03). Dronabinol did not alter sensation or tone. *CNR1 rs806378* (CC vs CT/TT) appeared to affect fasting proximal MI in all patients with IBS (*P*=.075). Dronabinol affected fasting distal MI in patients, regardless of *FAAHrs324420* variant (CA/AA vs CC) (*P*=.046); the greatest effects were observed among IBS-C patients with the *FAAH* CC variant (*P*=.045). Dronabinol affected fasting proximal MI in patients with IBS-D or -A with the variant *FAAH* CA/AA (*P*=.013).

Conclusion

In patients with IBS-D or -A, dronabinol reduces fasting colonic motility; *FAAH* and *CNR1* variants could influence the effects of this drug on colonic motility.

Keywords: sensory, motor, clinical trial, drug metabolism, pharmacodynamic

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INTRODUCTION

The effects of cannabinoids are mediated primarily through cannabinoid receptors. Two types of G protein coupled cannabinoid receptors, CB_1 and CB_2, have been identified and cloned[1–3]. There may be a third, as yet uncloned, cannabinoid receptor[4]. CB_1-immunoreactivity is located on normal colonic epithelium, smooth muscle, and the myenteric plexus, whereas both CB_1 and CB_2 receptors are expressed in plasma cells[5]. The endocannabinoid system consists of CB_1 and CB_2 receptors; the ligands of these receptors are anandamide and 2-arachidonyl glycerol (2-AG), and the ligand-inactivating enzymes are monoacylglycerol lipase (MGLL) and fatty acid amide hydrolase (FAAH)[6–9].

The activity of the endocannabinoid system varies between species and in different regions of the gastrointestinal (GI) tract within the same species. On the other hand, activation of CB_1 receptors coupled to cholinergic motor neurons inhibits excitatory nerve transmission in human colonic circular muscle[10] in vitro. In mice, endocannabinoids acting on myenteric CB_1 receptors tonically inhibit colonic propulsion[11]. In rodent models, activation of enteric cannabinoid CB_1 receptors inhibits gastric and small intestinal transit without altering intraluminal pressure or basal tone[12,13]. In a prior study in healthy volunteers, we have shown that dronabinol, a non-selective CB receptor agonist, inhibits gastric emptying and colonic motility in healthy humans[14,15]. The effects on colonic tone and phasic motility were observed with 7.5mg dronabinol, which was shown to induce drowsiness, lightheadedness and dizziness[15]. The 5mg dronabinol dose was more tolerable among healthy participants in our previous study. CB receptors are also involved in mediating nociception[16,17] and inflammation[18].

In this study, we assessed the effects of 5mg dronabinol on colonic sensory and motor functions in patients with irritable bowel syndrome (IBS) who were cannabinoid-naive. We hypothesized that dronabinol inhibits colonic motility and sensation in IBS, and that these inhibitory effects are affected by genetic variations in the CB_1 receptor and in rate-limiting enzymes of endocannabinoid degradation.

Our specific aims were: 1) to compare effects of single administrations of oral placebo, dronabinol 2.5mg, and dronabinol 5mg on colonic motility and sensation in cannabinoid-naive IBS patients; and 2) to examine potential influences of IBS subtypes and genetic variations in cannabinoid mechanisms on the effects of dronabinol treatment. In the latter aim, we examined effects of variations in critical genes for CB signaling (CBR type1), genes involved in metabolic breakdown of anandamide and 2-acylglycerol, FAAH and MGLL respectively, and *CYP2C9*3* which significantly alters the metabolism of dronabinol on colonic motor and sensory functions observed in response to treatment with dronabinol in IBS patients.

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MATERIALS AND METHODS

Study Design

This was a double-blind, randomized, placebo-controlled, parallel-group study (ClinicalTrials.gov identifier NCT01253408) of the pharmacodynamic effects of dronabinol on colonic sensory and motor functions of otherwise healthy human volunteer participants with IBS (ages between 18 and 67 years, and body mass index between 18 and 47 kg/m^2). The study was conducted in the Clinical Research Unit at Mayo Clinic in Rochester, MN (NIH CTSA grant RR0024150); the study started October 2008 and was completed November 2010. The study was approved by Mayo Clinic Institutional Review Board, and a data safety monitoring plan was established prior to starting the study.

Participants

All participants were recruited from a database of ~1000 patients with IBS who reside within 120 miles of Rochester, MN. Participants filled in a validated bowel disease questionnaire (BDQ, including questions to correspond to Rome III criteria)[19] and the Hospital Anxiety and Depression Inventory (HAD)[20]. The bowel disease questionnaire also included a somatic symptom checklist intended to identify somatization. All candidates were screened to ensure they were cannabinoid-naïve, and those who met the eligibility criteria for the study underwent a complete history and physical examination before enrollment. The trial flow is summarized in Figure 1.

Figure 1
Trial flow chart and baseline characteristics of study participants (Mean ± SEM, unless otherwise noted).

Ultimately, 75 otherwise healthy participants with IBS were enrolled, and 72 completed most studies characterizing the intermediate phenotypes. All females of childbearing potential had to

have a negative pregnancy test within 48 hours of study. Participants were randomized to one oral administration of placebo, dronabinol 2.5mg, or dronabinol 5mg, taken with water at the study center under supervision of study staff.

Randomization with 24 per treatment group was conducted by computer program. Allocation was concealed, and participants and investigators were blinded to all treatment assignments. The research pharmacist ensured the random allocation sequence was followed and that participants were assigned to the appropriate group. At study completion, the randomization code was communicated to the study statistician by the research pharmacist.

Pharmacology of Dronabinol

Dronabinol is a synthetic delta-9-tetrahydrocannabinol (Δ^9-THC). It is a non-selective cannabinoid agonist with affinity for both CB_1 and CB_2 receptors; 90–95% of the dose is absorbed after a single oral dose[21]. Due to the high first pass hepatic metabolism (primarily by microsomal hydroxylation) and lipid solubility, only 10–20% of the administered oral dose reaches the systemic circulation. The onset of action after oral administration is at 0.5 to 1 hour, and the peak effect is at 2 to 4 hours. The elimination phase follows a two-compartment model with an initial half-life of ~4 hours and a terminal half-life of 25–36 hours. Biliary excretion is the major route of elimination.

Experimental Protocol

After overnight bowel preparation using a standard polyethylene glycol-containing electrolyte solution (GoLytely, Braintree Laboratories, Inc., Braintree, MA) and a 12-hour fast to induce cleansing, a balloon-manometry assembly was placed in the mid-descending or upper sigmoid colon of each participant with the aid of unsedated left-side colonoscopy, guidewire placement and fluoroscopy. Details of the catheter, barostat, and conduct of sensation and motility testing are provided in the Appendix, and followed the procedures in prior studies[22,23].

The study medication was ingested, and 1 hour later the same colonic functions were assessed in the fasting state: the 30 minute post-drug tone first, followed by a second VAS scale to assess the levels of tension, relaxation, energy and drowsiness, and then the compliance and randomly ordered phasic distensions as previously done pre-drug. Subsequently, colonic tone and phasic pressure activity were measured for 30 minutes before and 1 hour after a standard 1000kcal liquid meal (750mL chocolate milkshake, 53% fat, 35% carbohydrate, 12% protein). When the recording was finished, the balloon was deflated and the tube was removed by gentle traction.

Data Analysis and Outcome Measures

Colonic compliance

We used a validated linear interpolation method to estimate compliance of the colon, summarized as the pressure at half-maximum volume (PR_{50} or PR_{50})[24].

Colonic motor function

Colonic tone was assessed operationally as the intracolonic balloon volume measured at the operating pressure. Tone was calculated by the baseline colonic volumes measured with the same intra-balloon operating pressure throughout the period of interest during fasting (before and after drug) or after the meal[25,26]. Using computer-based 10-minute mean volumes for the periods of interest and using the mean of each 10-minute observation in those periods, changes in colonic tone were calculated as absolute volume changes during fasting in response to the study medication and as the symmetric percent change in volume postprandially[23].

Colonic manometry

The same computer program was used to measure the postprandial phasic motor activity in the proximal and distal three manometric sensors. Because of variation in the location of the barostat balloon in the upper or lower descending colon, the phasic activity was summarized in each individual for the 3 sensors that were located in the distal descending and sigmoid colon. Data for the fasting period were compared with the two 30-minute periods after the 1000kcal meal was ingested. Colonic phasic pressure activity was summarized as a motility index (MI) where: MI= $\log_e$ (sum of amplitudes * number of contractions +1)

Colonic sensation

We recorded the pressure thresholds at which participants reported first perception, gas, and pain during the assessment of colonic compliance (ramp distention), and the intensity ratings recorded for gas and pain on 100mm VAS scales that were averaged over the 4 phasic pressure distensions (termed the mean sensation rating). We assessed stress and arousal scores while we assessed the effects of treatment on sensation. As there were no significant effects noted based on the scores of tension, relaxation, energy and drowsiness, the sensation results are provided without adjusting for these measurements.

Genotyping

DNA was extracted from whole blood as previously described[27]. The selection of candidate endocannabinoid genetic polymorphisms is included in the Appendix. Genotyping of *FAAH* rs324420, *CNR1* rs806378, and *MGLL* rs4881 was performed using Taqman™ SNP Genotyping assays (Applied Biosystems, Inc., Foster City, CA) in accordance with manufacturer instructions. In addition, we screened patients for the *CYP2C9* rs1057910 polymorphism (A1075C; Ile359Leu), also known as *CYP2C9*3*, since this variant significantly alters the metabolism of orally administered dronabinol[28], with a three-fold increase in plasma dronabinol levels in CC homozygotes, but only a modest increase in heterozygotes compared to "wildtype" AA homozygotes.

Sample Size Assessment

Appendix Table 1 shows the coefficients of variation and effect sizes demonstrable with n=24 per group, based on pre-treatment data or post-treatment placebo group data of motor and sensory endpoints for the participants in this study, using 80% power with a two-sided α of 0.05 in a two-sample t-test.

Statistical Analysis

The study statistician and the entire research team were blinded to treatment allocation until all analyses of motor and sensory endpoints had been completed. All subjects randomized were included in the analysis under the intention to treat (ITT) paradigm. Subjects with missing data had the corresponding values imputed using the overall subjects mean (or median). An analysis of covariance (ANCOVA) was used to assess treatment effects on colonic tone, compliance and VAS sensation rating scores, incorporating gender, BMI and the corresponding "baseline" or pre-drug value as covariates. An adjustment in the error degrees of freedom was made (subtracting one for each missing value imputed) to adjust the estimates of error variance in the ANCOVA models. In the overall analyses of treatment effects (i.e. ignoring IBS subgroup and genotype) and in the assessment of potential differential treatment effects among IBS subgroups, 4–7 missing values were imputed, depending on the particular quantitative trait or endpoint assessed (e.g. distal MI was missing in 7, and PR_{50} was missing in 4). In the pharmacogenetic analyses, 73 (*CNR1*), 71(*FAAH*), and 72(*MGLL*) of the 75 subjects had genotype status identified. Among the genotyped subjects, 1 to 4 missing values for the intermediate phenotype endpoints were imputed.

For the analysis of VAS sensation scores, analyses of the scores at the 40mmHg distension level and, separately, for the corresponding post-drug average (over all 4 distensions) were examined. The overall average baseline sensory rating score during the pre-drug study was the "corresponding" baseline value used as a covariate in these analyses.

A proportional hazards regression analysis was used to assess treatment effects on sensation thresholds, incorporating gender, BMI, and the corresponding pre-treatment sensory threshold value as covariates.

The analyses were repeated including IBS subgroup (combining IBS-D and IBS-A, since the latter have been shown to have accelerated transit at 48hours, similar to IBS-D)[29] and, separately, the *CNR1, FAAH* and *MGLL* genotypes (dominant genetic model grouping the minor allele homozygotes together with heterozygotes) as covariates, along with the corresponding treatment by subgroup interaction terms. Due to the small minor allele frequency (MAF) of the *MGLL* rs4881 SNP, for both the *CNR1* rs806378 and *FAAH* rs324420 SNPs we assessed potential differential drug vs. placebo treatment effects by combining the 2.5 and 5mg dronabinol doses. Finally exploratory analyses incorporating IBS subtype and each genotype subtype (separately) were also examined to check for potential differential treatment effects by IBS subtypes and candidate genotypes.

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RESULTS

Participants and Compliance with Medication

The trial flow is shown in Figure 1. Seventy-five IBS volunteers meeting the entry criteria were screened and randomized, with a total of 72 completing the study. A total of 27 volunteers

randomly received placebo, 24 received dronabinol 2.5mg, and 24 received dronabinol 5mg. The table in Figure 1 summarizes patient demographics by treatment groups. No clinically important differences in age, sex, body mass index, barostat operating pressure, or pre-drug fasting colonic tone were observed between treatment groups.

CYP2C9 Polymorphism

Genotyping of our study cohort for *CYP2C9* rs1057910 revealed 62 participants with AA and the remaining 10 with CA genotypes. Subjects were equally distributed by genotype across the three treatment groups. As there were no CC homozygotes, who would be expected to have different blood levels of dronabinol in contrast to heterozygotes who had minimal changes in blood levels[28], we did not expect clinically significant variations in plasma dronabinol levels or in median area under the concentration curve across treatment groups. Therefore, there would be no impact of individual metabolism of dronabinol on the study endpoints.

Effects of Dronabinol on Colonic Compliance in Overall and Patient Subgroups

There was overall borderline treatment effect on colonic compliance (p=0.058), which was most pronounced in the dronabinol 5mg group (Table I). The reduction in Pr_{50} reflects an increase in compliance of the colon in response to dronabinol. In addition, the effect on compliance was prominent in the IBS-D/A subgroup (p=0.03 unadjusted for 2 subgroup comparisons, that is, IBS-C and IBS-D/A). Similarly, the effect on compliance within the IBSD/A subgroup was most robust with the 5mg dronabinol dose (Figure 2).

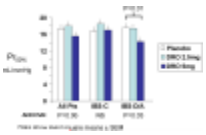

Figure 2
Effect of dronabinol on colonic compliance. Data reported are least squares (LS) means and standard errors (SEM). The error bars are based on the square root of the ratio: pooled estimate of residual error variance (across all subgroups from the ANCOVA) **...**

Table I
Effect of Dronabinol on Colonic Compliance, Proximal and Distal Left Colon Motility Ind Colonic Tone, and sensation ratings in response to distensions

	Placebo			Dronabinol 2.5mg		
	All IBS	IBS-C	IBS-D/A	All IBS	IBS-C	IBS
CYP2C9 3s with CA/AA genotype	3/22	1/8	2/14	3/19	2/10	
Compliance Pr_{50} (mL/mmHg)	17.3±0.9	16.6±1.4	17.6±1.0	18.0±1.0	18.5±1.1	17.
Fasting tone, mL	105.3±4.8	98.8±7.3	107.1±5.3	107.6±5.2	110.0±6.0	100
PP relative Δ tone (0-30 min) / fasting	30.0±5.0	31.7±7.7	27.1±5.6	32.8±5.5	32.8±6.3	32.

Table I
Effect of Dronabinol on Colonic Compliance, Proximal and Distal Left Colon Motility Index, Fasting and Postprandial (PP) Change in Colonic Tone, and sensation ratings in response to distensions

Effects of Dronabinol on Fasting and Postprandial Colonic Tone

Fasting pre-treatment colonic tone was not significantly different among the three groups (Figure 1). There were no significant effects of dronabinol treatment on fasting or postprandial colonic tone (Table I).

Effects of Dronabinol on Phasic Colon Contractile Activity

Phasic contractility during fasting and postprandially was compared for the upper 3 pressure sensors corresponding to the upper descending colon (henceforth called proximal left colon) and separately for the lower 3 pressure sensors corresponding to the junction of descending colon, sigmoid and rectum (henceforth called distal left colon) as recorded in all individuals. Before treatment, fasting colonic motility was not different among the three treatment groups (data not shown).

Dronabinol significantly reduced proximal left colon MI (overall effect p=0.05) and tended to reduce post-drug colon MIs (overall effect, p=0.08, Table I and Figure 3). In each case, the effect was predominantly attributed to the dronabinol 5mg dose [proximal colon, p=0.046 (adjusted) and distal colon, p=0.13 (adjusted)].

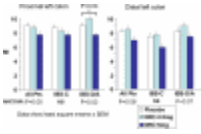

Figure 3
Effect of dronabinol on colonic phasic pressure activity. Data reported are least squares (LS) means and standard errors (SEM). The error bars are based on the square root of the ratio: pooled estimate of residual error variance (across all subgroups **...**

Overall treatment effects on proximal colon MI were significant in patients with IBS-D/A (p=0.044, after adjustment for two tests for the two IBS subgroups), but not in IBS-C (Figure 3), with the predominant effect observed with the dronabinol 5mg dose.

Effects on Colonic Sensory Function during Phasic and Ramp Distensions

Sensation thresholds for gas and pain during ramp distensions were not different among the treatment groups over the entire range of pressures tested (data not shown).

Sensation scores for pain and gas in response to high distension pressures were not significantly different among treatment groups (Table I). No overall treatment effects on mean post-drug VAS sensation rating scores were detected for sensation of gas (p=0.67) or pain (p=0.60).

Effect on Central Arousal and Stress

Appendix Table 2 shows effects on states of tension, relaxation, energy, and drowsiness, which illustrate the lack of significant central effects of the 2.5 and 5mg dronabinol doses.

Pharmacogenetics: Treatment by Genotype Interaction Effects for the Entire IBS Group

CNR1 rs806378

In the CT/TT genotype (in contrast to the CC genotype), somewhat higher sensation ratings of gas and pain were observed in response to dronabinol versus placebo (Appendix Table 3A, which shows effects of 2.5 and 5mg doses of dronabinol separately). However, significant differential treatment effects were not detected (p=0.39 for gas sensation and p=0.43 for pain sensation with the pooled analyses of effects of 2.5 and 5mg dronabinol).

In addition, in the CC genotype (but not CT/TT), a more pronounced dronabinol induced reduction in fasting proximal colon MI was observed (p=0.11 for CC vs. p=0.99 for CT/TT). The effects of *CNR1* rs806378 genotype and dronabinol dose interaction on main sensation and motility endpoints are shown in Table II.

Table II
Effects of CNR1 rs806378 Genotype and Dronabinol Dose Interaction on Main Sensation and Motility Endpoints

Effect	(Mean) Gas Sensation Ratings	(Mean) Pain Sensation Ratings	Proximal Fasting MI	Distal Fasting MI
Gene by treatment (interaction effect)	0.40	0.56	0.49	0.44
CC (n=18 on PLA) overall treatment effect	0.53	0.62	0.037	0.038
2.5 mg DRO (n=12) vs. PLA	0.48	0.59	0.85	0.34
5 mg DRO (n=14) vs. PLA	0.60	0.59	0.016	0.064
CT/TT (n=8 on PLA) overall treatment effect	0.56	0.60	0.67	0.79

Table II
Effects of *CNR1* rs806378 Genotype and Dronabinol Dose Interaction on Main Sensation and Motility Endpoints

No differential treatment effects on compliance associated with *CNR1* status were detected (interaction, p=0.93; treatment effects in CC, p=0.59; treatment effects in CT/TT, p=0.63).

FAAH rs324420

In the CC genotype, a reduced postprandial tone response was observed during treatment with dronabinol, while in the CA/AA genotype, increased postprandial tone (calculated as the relative change in colonic tone, fasting compared to fed tone) was observed in response to dronabinol (test for drug by genotype interaction, p=0.10).

No other differential treatment effects by *FAAH* genetic status were noted (Appendix Table 3A).

MGLL rs4881

No differential treatment effects on motor or sensory functions by *MGLL* rs4881 genotype status were detected.

Treatment by IBS Subgroup by Genotype Interactions (Appendix Table III B and C)

CNR1 rs806378

Treatment effects were suggested with genotype CC in IBS-D/A for compliance (p=0.066) and proximal left colon MI (p=0.075, Figure 4).

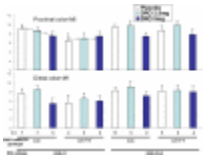

Figure 4
Pharmacogenetics of *CNR1* rs806378 and colonic motility index. Treatment effects were most prominently suggested in IBS-D/A and the *CNR1* rs806378 genotype CC for proximal left colon MI (p=0.075). Data reported are least squares (LS) means and standard **...**

Differential treatment effects among *CNR1* rs806378 genotypes (CC vs. CT/TT) and IBS subtypes were observed for fasting colon tone (p=0.047) (see Appendix Table III B and C), with the most pronounced treatment effects observed with the CC genotype in IBS-C (p=0.09).

Although the overall test for treatment group by IBS subgroup by *CNR1* genotype interaction was not significant (p=0.11), overall treatment effects (i.e. differences among the three treatment groups) on postprandial (relative change from fasting) tone were borderline significant (p=0.084, unadjusted) within the IBS-C and CT/TT subgroup, but not for any of the other subtype/genotype combinations.

FAAH rs324420

Differential treatment effects among *FAAH* rs324420 genotypes (CC vs. CA/AA) and IBS subtypes (Figure 5) were observed for proximal left colon MI (p=0.09), most pronounced in IBS-D/A and CA/AA (p=0.013), and for distal left colon MI (p=0.046), most pronounced in IBS-C and CC (p=0.045).

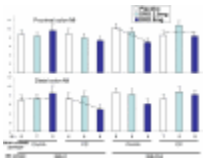

Figure 5
Pharmacogenetics of *FAAH* and colonic motility index. Differential treatment effects among *FAAH* rs324420 genotypes (CC vs. CA/AA) and IBS subtypes were observed for proximal left colon MI, (p=0.09), and were most pronounced in IBS-D/A and CA/AA (p=0.013). **...**

MGLL rs4881

The analyses for MGLL did not detect any striking "differential" treatment effects, but the minor allele frequency was rather low (1 CC, 12 CT, and 59 TT). There were some suggestions of differential treatment effects for mean VAS gas scores (p=0.12), mean VAS pain scores (p=0.08), and a possibly higher pain sensation threshold in CT/CC subjects on drug; however,

there were only 6 in this subgroup. There also appeared to be an "overall" (irrespective of treatment) modest association of *MGLL* subtype, with relative change in colonic tone and proximal fasting (post-drug) MI.

No other differential treatment effects were associated with IBS and genotype subgroups.

Adverse Effects

The most frequent adverse effects were: drowsy/tired 23%; flushing/hot 19%; headache 13%; dizzy/lightheaded 11%; loopy/foggy thinking 11%; elevated heart rate 11%; relaxed/dream-like state 9%; nausea 8%, dry mouth and eyes 7%. The adverse effects are broken down by group in Appendix Table 4. The only adverse effect which was more common with dronabinol than placebo was loopy/foggy thinking (p=0.009 by Fisher's exact test).

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DISCUSSION

This study demonstrates cannabinoid modulation of colonic compliance and fasting colonic motility in patients with IBS; specifically, a single dronabinol dose of 5mg acutely increased colonic compliance and reduced fasting colonic motility in the subgroups of IBS-D and IBS-A patients. Previously, dronabinol had been demonstrated to increase colonic compliance and to inhibit colonic motility and tone in healthy male or female volunteers[14]. Dronabinol also delayed gastric emptying in female, but not male healthy subjects[15]. Our current study involving >90% female IBS patients characterizes dronabinol's effects on colonic motor and sensory functions.

Using a barostat-manometry assembly, we observed an increase in colonic compliance and a decrease in proximal left colon phasic motility index with dronabinol treatment. These two effects are internally consistent and reflect the inhibition of tonic excitatory motor or activation of inhibitory neural mechanisms by the non-selective cannabinoid agonist. In contrast to dronabinol's effects on colonic motor function observed with the 7.5mg dronabinol dose in healthy volunteers[14], the 5mg dose of dronabinol in this study did not significantly inhibit fasting colonic tone or the motor response to feeding in IBS patients. The drug dose is clearly critical, since the 2.5mg dose in this study had no effect, while the 7.5mg dose used previously[14] inhibited colonic tone, increased colonic sensations, and induced central effects such as lightheadedness consistent with known responses to the cannabinoid receptor agonist[14]. The observed effects of a single administration of 5mg dronabinol, together with the known expression of cannabinoid receptors on cholinergic neurons in the brain stem, stomach and colon, are consistent with the hypothesis that dronabinol may be inhibiting colonic muscle excitation via cholinergic neurons in the central and enteric nervous systems[30]. Cannabinoid receptor modulation is a potential target for therapy in diseases associated with accelerated transit[29] or increased colonic motor function in patients with IBS-D[31,32].

In contrast to the effects of a single dose of 7.5mg dronabinol noted in healthy subjects, a single 5mg dose in IBS patients did not increase stress, arousal, or colonic sensations of gas and pain measured as either sensory thresholds or visual analog ratings in response to random-order

phasic distensions. Identification of a peripheral effect on colonic motor function without increasing unwanted sensations of gas or pain, as well as alterations in affect or arousal is critically important to the development of cannabinoid agents as potential therapy in IBS. In agreement with a recent study on dronabinol's effects on visceral perception to rectal balloon distension[33], our study also did not show any potentially beneficial changes in visceral perception to balloon distension in the left colon.

Our data show that significant effects of dronabinol on colonic compliance and motility were predominantly observed with the 5mg dose in those IBS patients who experience diarrhea (IBS-D and IBS-A). Of note, about 48% of patients with IBS-D have accelerated colonic transit at 24 or 48 hours and, as a group, patients with IBS-A have accelerated transit at 48 hours compared to healthy controls[29]. Inhibition of colonic motility by dronabinol may provide potential benefit to those IBS-D and IBS-A patients with accelerated transit.

Given the effects of CB_1 receptor modulation on colonic functions[14] and the association of *FAAH* genetic variation with diarrhea and colonic transit in IBS-D patients[34], we conducted a pharmacogenetic analysis exploring the influence of genetic variation in the CB_1 receptor and in the rate-limiting catabolic enzymes for anadamide (FAAH) and 2-acylglycerol (MAGL), the two primary endocannabinoids in humans. Our data suggest that effects of dronabinol on colonic compliance and proximal colonic motility may be influenced by genetic variations in *FAAH* and *CNR1*. We did not observe any significant modulation by variation in *MGLL*, but our analysis of *MGLL* was compromised by the low minor allele frequency of rs4881. Overall, our pharmacogenetic data lend support to the hypothesis that a genetic basis accounts for differences in effects on colonic functions by drugs targeting cannabinoid receptors or the metabolism of anadamide. Therefore, future studies of more selective cannabinoid receptor agonists or antagonists may be more informative if pharmacogenetic analysis is included to help identify individuals more likely to benefit from cannabinoid or anti-cannabinoid medications.

Cannabidiol analogs devoid of the central effects on cannabinoid receptor activation have been proposed as therapy for diarrheal diseases[35,36]. In contrast, a cannabinoid receptor antagonist may oppose the inhibition of cholinergic mechanisms by endogenous cannabinoids, which may relieve constipation via acceleration of colonic transit and enhancement of intestinal secretion. Izzo et al. showed in a mouse model that the CB_1 antagonist, rimonabant (also known as SR141716A, 0.1–5mg/kg, i.p.), increased defecation, gastrointestinal transit, and fluid accumulation in the colon. These effects were inhibited by atropine (1mg/kg, i.p.), but not by the ganglion blocking agent, hexamethonium, or by antagonists of NK_1 and NK_2 receptors[37]. Interestingly, in clinical trials of rimonabant used in aiding nicotine cessation or in treating obesity, diarrhea was 2 to 2.4 times more frequent among those treated with the drug than with placebo, suggesting accelerated colonic transit and/or enhanced mucosal secretion resulting from CB_1 blockade[38,39].

We did not observe increase in sensation with the 5mg dronabinol dose in IBS, in contrast to the effects of the 7.5mg dose in healthy subjects. This is relevant because any beneficial effects on colonic motor function could potentially be negated by increased sensations of gas or pain. Increased awareness of surroundings was reported more frequently in patients receiving delta-9-THC[40]. On the other hand, Sanson et al.[17] suggested that cannabinoid effects on increasing

sensation during colonic distension in rats with inflamed colon were mediated peripherally. Importantly, the increased compliance induced by dronabinol did not compromise our assessment of sensory effects since our study used pressure-based distensions to avoid the erroneous interpretation of sensory changes as would occur with sensory ratings measured using volume-based distensions. Further studies are needed to explore the effects of cannabinoid receptor modulation in the sensory neuraxis in humans after repeated administrations of cannabinoid agents.

The strengths of our study include our research team's extensive experience with methods measuring colonic motility and sensation, and the trial generalizability as shown by sample size with adequate power to detect clinically meaningful effects on primary endpoints, multiple medication doses studied, analysis by IBS subgroups based on predominant bowel function, and inclusion of pharmacogenetic analysis to assess whether dronabinol's effects may be influenced by genetic variations in cannabinoid signaling or metabolism..

The weaknesses of this study include assessment of a single administration of dronabinol and the non-selective nature of dronabinol for CB_1 and CB_2 receptors. Our study had sufficient power to detect treatment effects on motor and sensory responses based on 24 patients per group; the power was lower for symptom subgroups of IBS and for subgroups based on genotypes, where the number of participants in each group divided according to genotype ranged from 2 to 11. Our study also had limited power to detect differences in sensation thresholds due to the large coefficient of variation in these endpoints when compared to the coefficients for motility indices and sensation ratings. Therefore, the pharmacogenetic results, in particular, are to be viewed as only hypothesis-generating. In addition, knowing the blood levels of dronabinol may also have enhanced the interpretation of the associations of the genetic variations of the effects of dronabinol.

In summary, our study shows that the non-selective cannabinoid receptor agonist, dronabinol, inhibits fasting colonic motility and enhances colonic compliance in IBS, particularly in patients with IBS-D and IBS-A. These effects may be better harnessed with selective cannabinoid receptor agonists and antagonists. A selective CB_1 agonist, in particular, may have potential as therapy in diarrhea-positive IBS patients. Further studies to assess the therapeutic role of dronabinol and other cannabinoid receptor agonists in IBS are warranted.

Go to:

Supplementary Material

01

Click here to view.(88K, doc)

02

Click here to view.(78K, ppt)

Go to:

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Footnotes

Disclosures: The authors have no conflicts of interest to report.

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REFERENCES

1. Howlett AC. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol Rev. 2002;54:161–202. [PubMed]
2. Matsuda LA, Lolait SJ, Brownstein MJ, et al. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature. 1990;346:561–564. [PubMed]
3. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature. 1993;365:61–65. [PubMed]
4. Begg M, Pacher P, Batkai S, et al. Evidence for novel cannabinoid receptors. Pharmacol Ther. 2005;106:133–145. [PubMed]
5. Database of Single Nucleotide Polymorphisms (dbSNP) National Center for Biotechnology Information, National Library of Medicine; Bethesda (MD: (dbSNP Build ID: {132}). Available from: http://www.ncbi.nlm.nih.gov/SNP/
6. Devane WA, Hanus L, Breuer A, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science. 1992;258:1946–1949. [PubMed]
7. Hillard CJ. Biochemistry and pharmacology of the endocannabinoids arachidonylethanolamide and 2-arachidonylglycerol. Prostaglandins Other Lipid Mediat. 2000;61:3–18. [PubMed]
8. Mechoulam R, Benshabat S, Hanus L, et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem Pharmacol. 1995;50:83–90. [PubMed]

9. Sugiura T, Kondo S, Sukagawa A, et al. 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. Biochem Biophys Res Commun. 1995;215:89–97. [PubMed]
10. Hinds NM, Ullrich K, Smid SD. Cannabinoid 1 (CB(1)) receptors coupled to cholinergic motorneurones inhibit neurogenic circular muscle contractility in the human colon. Br J Pharmacol. 2006;148:191–199. [PMC free article] [PubMed]
11. Pinto L, Izzo AA, Cascio MG, et al. Endocannabinoids as physiological regulators of colonic propulsion in mice. Gastroenterology. 2002;123:227–234. [PubMed]
12. Izzo AA, Mascolo N, Capasso R, et al. Inhibitory effect of cannabinoid agonists on gastric emptying in the rat. Naunyn Schmiedebergs Arch Pharmacol. 1999;360:221–223. [PubMed]
13. Shook JE, Burks TF. Psychoactive cannabinoids reduce gastrointestinal propulsion and motility in rodents. J Pharmacol Exp Therapeutics. 1989;249:444–449. [PubMed]
14. Esfandyari T, Camilleri M, Busciglio I, et al. Effects of a cannabinoid receptor agonist on colonic motor and sensory functions in humans: a randomized, placebo-controlled study. Am J Physiol. 2007;293:G137–G145. [PubMed]
15. Esfandyari T, Camilleri M, Ferber I, et al. Effect of a cannabinoid agonist on gastrointestinal transit and postprandial satiation in healthy human subjects: a randomized, placebo-controlled study. Neurogastroenterol Motil. 2006;18:831–838. [PubMed]
16. Pacher P, Batkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev. 2006;58:389–462. [PMC free article] [PubMed]
17. Sanson M, Bueno L, Fioramonti J. Involvement of cannabinoid receptors in inflammatory hypersensitivity to colonic distension in rats. Neurogastroenterol Motil. 2006;18:949–956. [PubMed]
18. Klein TW. Cannabinoid-based drugs as anti-inflammatory therapeutics. Nat Rev Immunol. 2005;5:400–411. [PubMed]
19. Talley NJ, Phillips SF, Wiltgen CM, et al. Assessment of functional gastrointestinal disease: the bowel disease questionnaire. Mayo Clin Proc. 1990;65:1456–1479. [PubMed]
20. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361–370. [PubMed]
21. MICROMEDEX H. Micromedex. 2005. Physician's Desk Reference.
22. Hammer HF, Phillips SF, Camilleri M, et al. Rectal tone, distensibility, and perception: reproducibility and response to different distensions. Am J Physiol. 1998;274:G584–G590. [PubMed]
23. Viramontes BE, Malcolm A, Camilleri M, et al. Effects of an alpha(2)-adrenergic agonist on gastrointestinal transit, colonic motility, and sensation in humans. Am J Physiol. 2001;281:G1468–G1476. [PubMed]
24. Floyd BN, Camilleri M, Andresen V, et al. Comparison of mathematical methods for calculating colonic compliance in humans: power exponential, computer-based and manual linear interpolation models. Neurogastroenterol Motil. 2008;20:330–335. [PMC free article] [PubMed]
25. Bharucha AE, Camilleri M, Zinsmeister AR, et al. Adrenergic modulation of human colonic motor and sensory function. Am J Physiol. 1997;273:G997–G1006. [PubMed]
26. Delgado-Aros S, Chial HJ, Camilleri M, et al. Effects of a kappa-opioid agonist, asimadoline, on satiation and GI motor and sensory functions in humans. Am J Physiol. 2003;284:G558–G566. [PubMed]

27. Chiang KP, Gerber AL, Sipe JC, et al. Reduced cellular expression and activity of the P129T mutant of human fatty acid amide hydrolase: evidence for a link between defects in the endocannabinoid system and problem drug use. Hum Mol Genet. 2004;13:2113–2119. [PubMed]
28. Sachse-Seeboth C, Pfeil J, Sehrt D, et al. Interindividual variation in the pharmacokinetics of Delta9-tetrahydrocannabinol as related to genetic polymorphisms in CYP2C9. Clin Pharmacol Ther. 2009;85:273–276. [PubMed]
29. Camilleri M, McKinzie S, Busciglio I, et al. Prospective study of motor, sensory, psychologic, and autonomic functions in patients with irritable bowel syndrome. Clin Gastroenterol Hepatol. 2008;6:772–781. [PMC free article] [PubMed]
30. Sibaev A, Yüce B, Kemmer M, et al. Cannabinoid-1 (CB1) receptors regulate colonic propulsion by acting at motor neurons within the ascending motor pathways in mouse colon. Am J Physiol. 2009;296:G119–G128. [PubMed]
31. Choi MG, Camilleri M, O'Brien MD, et al. A pilot study of motility and tone of the left colon in patients with diarrhea due to functional disorders and dysautonomia. Am J Gastroenterol. 1997;92:297–302. [PubMed]
32. Chey WY, Jin HO, Lee MH, et al. Colonic motility abnormality in patients with irritable bowel syndrome exhibiting abdominal pain and diarrhea. Am J Gastroenterol. 2001;96:1499–1506. [PubMed]
33. Klooker TK, Leliefeld KE, Van Den Wijngaard RM, et al. The cannabinoid receptor agonist delta-9-tetrahydrocannabinol does not affect visceral sensitivity to rectal distension in healthy volunteers and IBS patients. Neurogastroenterol Motil. 2011;23:30–35. [PubMed]
34. Camilleri M, Carlson P, McKinzie S, et al. Genetic variation in endocannabinoid metabolism, gastrointestinal motility and sensation. Am J Physiol. 2008;294:G13–G19. [PubMed]
35. Fride E, Feigin C, Ponde DE, et al. (+)-Cannabidiol analogues which bind cannabinoid receptors but exert peripheral activity only. Eur J Pharmacol. 2004;506:179–188. [PubMed]
36. Fride E, Ponde D, Breuer A, et al. Peripheral, but not central effects of cannabidiol derivatives: Mediation by CB(1) and unidentified receptors. Neuropharmacology. 2005;48:1117–1129. [PubMed]
37. Izzo AA, Mascolo N, Borrelli F, et al. Defaecation, intestinal fluid accumulation and motility in rodents: implications of cannabinoid CB1 receptors. Naunyn Schmiedebergs Arch Pharmacol. 1999;359:65–70. [PubMed]
38. Fernandez JR, Allison DB. Rimonabant. Curr Opin Investig Drugs. 2004;5:430–435. [PubMed]
39. Van Gaal LF, Rissanen AM, Scheen AJ, et al. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet. 2005;365:1389–1397. [PubMed]
40. Buggy DJ, Toogood L, Maric S, et al. Lack of analgesic efficacy of oral delta-9-tetrahydrocannabinol in postoperative pain. Pain. 2003;106:169–172. [PubMed]

Cannabis use amongst patients with inflammatory bowel disease.

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Abstract

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.

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Cannabis use provides symptom relief in patients with inflammatory bowel disease but is associated with worse disease prognosis in patients with Crohn's disease.

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Abstract

BACKGROUND:

Cannabinoids are used by patients with inflammatory bowel disease (IBD) to alleviate their symptoms. Little is known on patient motivation, benefit, or risks of this practice. Our aim was to assess the extent and motives for Cannabis use in patients with IBD and the beneficial and adverse effects associated with self-administration of Cannabis.

METHODS:

Consecutive patients with IBD (n = 313) seen in the University of Calgary from July 2008 to March 2009 completed a structured anonymous questionnaire covering motives, pattern of use, and subjective beneficial and adverse effects associated with self-administration of Cannabis. Subjects who had used Cannabis specifically for the treatment of IBD or its symptoms were compared with those who had not. Logistic regression analysis was used to identify variables predictive of poor IBD outcomes, specifically surgery or hospitalization for IBD.

RESULTS:

Cannabis had been used by 17.6% of respondents specifically to relieve symptoms associated with their IBD, the majority by inhalational route (96.4%). Patients with IBD reported that Cannabis improved abdominal pain (83.9%), abdominal cramping (76.8%), joint pain (48.2%), and diarrhea (28.6%), although side effects were frequent. The use of Cannabis for more than 6 months at any time for IBD symptoms was a strong predictor of requiring surgery in patients with Crohn's disease (odds ratio = 5.03, 95% confidence interval = 1.45-17.46) after correcting for demographic factors, tobacco smoking status, time since IBD diagnosis, and biological use. Cannabis was not a predictor for hospitalization for IBD in the previous year.

CONCLUSIONS:

Cannabis use is common in patients with IBD and subjectively improved pain and diarrheal symptoms. However, Cannabis use was associated with higher risk of surgery in patients with Crohn's disease. Patients using Cannabis should be cautioned about potential harm, until clinical trials evaluate efficacy and safety.

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[Efficacy, tolerability, and safety of cannabinoids in gastroenterology: A systematic review].

[Article in German]

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Abstract

BACKGROUND:

The medical use of cannabis is discussed in gastroenterology for inflammatory bowel diseases (IBD), irritable bowel syndrome (IBS), and chronic pancreatitis.

MATERIALS AND METHODS:

A systematic literature search until March 2015 was performed in the databases Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, www.cannabis-med.org , and clinicaltrials.gov. Randomized controlled trials (RCT) investigating herbal cannabis and/or pharmaceutical cannabinoids in IBD, IBS, or chronic pancreatitis with a study duration of ≥ 4 weeks and a sample size of at least n = 10 per study arm were identified. Clinical outcomes comprised efficacy (pain, nausea, appetite/weight, diarrhea, health-related quality of life, and remission rates for IBD), tolerability (drop-out rate due to side effects), and safety (severe side effects). Methodology quality of RCTs was evaluated with the Cochrane Risk of Bias Tool.

RESULTS:

Only one RCT treating 21 patients with Crohn's disease and herbal cannabis was identified. The study revealed no significant differences of remission rate because of low statistical power. However, there was a clear tendency for less abdominal pain and improved appetite with medical cannabis. The methodological risk of the study was high. Furthermore, results of two RCTs investigating synthetic cannabis in IBD and chronic pancreatitis, respectively, have not yet been released. No RCT for IBS was found. Several case reports described cannabis-induced acute pancreatitis.

CONCLUSIONS:

Cannabis may be useful for symptom relief in Crohn's disease such as pain, nausea, and loss of appetite. However, studies with high methodological quality, sufficient sample size, and study duration are mandatory to determine potential therapeutic effects and risks of cannabis in gastroenterology. Currently, use of tetrahydrocannabinol to alleviate symptoms such as pain and appetite loss in Crohn's disease should only be considered in individual patients after failure of established medical therapies and only after careful risk-benefit assessment.

KEYWORDS:

Cannabis; Inflammatory bowel disease; Irritable bowel syndrome; Pancreatitis, chronic; Randomized controlled trials

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Cannabinoids for treating inflammatory bowel diseases: where are we and where do we go?

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Abstract

Fifty years after the discovery of Δ^9-tetrahydrocannabinol (THC) as the psychoactive component of Cannabis, we are assessing the possibility of translating this herb into clinical treatment of inflammatory bowel diseases (IBDs). Here, a discussion on the problems associated with a potential treatment is given. From first surveys and small clinical studies in patients with IBD we have learned that Cannabis is frequently used to alleviate diarrhea, abdominal pain, and loss of appetite. Single ingredients from Cannabis, such as THC and cannabidiol, commonly described as cannabinoids, are responsible for these effects. Synthetic cannabinoid receptor agonists are also termed cannabinoids, some of which, like dronabinol and nabilone, are already available with a narcotic prescription. Areas covered: Recent data on the effects of Cannabis/cannabinoids in

experimental models of IBD and in clinical trials with IBD patients have been reviewed using a PubMed database search. A short background on the endocannabinoid system is also provided. Expert commentary: Cannabinoids could be helpful for certain symptoms of IBD, but there is still a lack of clinical studies to prove efficacy, tolerability and safety of cannabinoid-based medication for IBD patients, leaving medical professionals without evidence and guidelines.