Cannabis and the Gastrointestinal Tract

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ABSTRACT - Cannabis has been used for its medicinal purposes since ancient times. Its consumption leads to the activation of Cannabis receptors CB1 and CB2 that, through specific mechanisms can lead to modulation and progression of inflammation or repair. The novel findings are linked to the medical use of Cannabis in gastrointestinal (GI) system. **PURPOSE:** The objective of the present paper is to elucidate the role of Cannabis consumption in GI system. An additional aim is to review the information on the function of Cannabis in non-alcoholic fatty liver disease (NAFLD). **METHODS AND RESULTS:** This review summarizes the recent findings on the role of cannabinoid receptors, their synthetic or natural ligands, as well as their metabolizing enzymes in normal GI function and its disorders, including irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) and possible adverse events. The synergism or antagonism between Cannabis' active ingredients and the "entourage" plays a role in the efficacy of various strains. Some elements of Cannabis may alter disease severity as over-activation of Cannabis receptors CB1 and CB2 can lead to changes of the commensal gut flora. The endocannabinoid system (ECS) contributes to gut homeostasis. The ability of ECS to modulate inflammatory responses demonstrates the capacity of ECS to preserve gastrointestinal (GI) function. Alterations of the ECS may predispose patients to pathologic disorders, including IBD. Clinical studies in IBD demonstrate that subjects benefit from Cannabis consumption as seen through a reduction of the IBD-inflammation, as well as through a decreased need for other medication. NAFLD is characterized by fat accumulation in the liver. The occurrence of inflammation in NAFLD leads to non-alcoholic-steatohepatitis (NASH). The use of Cannabis might reduce liver inflammation. **CONCLUSIONS:** With limited evidence of efficacy and safety of Cannabis in IBD, IBS, and NAFLD, randomized controlled studies are required to examine its therapeutic efficacy. Moreover, since long term use of the plant leads to drug use disorders the patients should be followed continuously.

INTRODUCTION

Genus *Cannabis (Family Cannabicae)* was classified into three species: *Cannabis sativa, Cannabis ruderalis* and *Cannabis indica*. Carl Linné described *Cannabis sativa*.

The Cannabis plant has been valued since ancient times. A concoction, which included Cannabis, was used by Jewish priests for ceremonial sacrifice is described in The Book of Numbers. In India, Ayurvedic texts describe Cannabis' anti-inflammatory, antiseptic, and anti-convulsing properties. The Chinese compendium of herbal medicine, "Shen Nung Pen Ts'ao Ching" (~2800 BC), first published the medicinal values of the plant and recommended it be consumed as tea for gout, malaria, rheumatism, neuropatic pain, epilepsy and poor memory.

The Persian physician-scientist Avicenna, in his book *The Canon,* advocated for its use as an analgesic for headaches (6). Additionally, the Persian physician al-Razi (Rhazes) (ca. 865-925) prescribed hemp leaves as a cure for ear ailments, dandruff, flatulence and epilepsy (7). "Majoon Birjandi," an Iranian folk medicine which contains Cannabis, is still used in Eastern Iran today (8). Cannabis has also traditionally been used throughout the Arabian Peninsula, Southeast Asia, South Africa and Central America (1-5).

The Cannabis plant contains 60 aromatic hydrocarbon compounds known as cannabinoids, including delta-9-tetra-hydocannabinol (THC), which is primarily psychotropic. Another element, Cannabidiol (CBD), is efficacious in inflammation, motility and analgesia. Cannabigerol, the effect of which is still to be determined (9,10), completes the picture.

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Abbreviations
ALD-alcoholic liver disease; CBD - Cannabidiol, CB1 and CB2 - Cannabis receptors, CD -Crohn's disease, CNS- Central Nervous System; ECS - endocannabinoid system, FAAH -fatty acid amide hydrolase, GI-gastrointestinal system, IBD - inflammatory bowel disease, IBS- Inflammatory bowel syndrome, NAPE-PLD - N-acyl-phosphatidyl-ethanolamine-phospholipase - D, NASH-non-alcoholic steatohepatitis; PPAR-gamma- peroxisome proliferator activated receptor gamma, UC -ulcerative colitis, THC- delta-9-tetra-hydocannabinol

Key words
Cannabis receptors, endocannabinoids, gut microbiota, inflammatory bowel disease, Cannabis use disorders, non-alcoholic steatohepatitis, pancreas

In order to be pharmacologically usable, the active ingredients have to be consistent in concentration and potency. Robust laboratory testing is required at several points.

PHARMACODYNAMICS AND PHARMACOKINETICS

Throughout the 1960s and 1970s, Israeli scientist Raphael Mechoulam, and his team, isolated and elucidated the structure of the major cannabinoid constituents, including Δ(9)-tetrahydrocannabinol (Δ(9)-THC) in *Cannabis sativa* (11). The two cannabinoid receptors were identified in the1980s and the early 1990s and the endocannabinoid system identification led to advances in understanding diseases and therapies (12). The THC agent acts mainly *via* two types of cannabinoid receptors, namely CB1 and CB2 receptors (12-14). CB1 receptors are predominantly located in the central and peripheral neurons, including the cortex, hippocampus, basal nuclei and amygdala, as well as the enteric nervous system along the gastrointestinal (GI) tract (such as the epithelium of the GI tract) and sensory terminals of vagal and spinal neurons. Activation of the CB1 receptors decreases motility along the GI tract mainly by inhibiting ongoing contractile transmitter release (15-18).

Cannabinoids can cause a wide variety of physiological reactions such as GI motility, intestinal secretions, inhibition of inflammatory mediators, promotion of fibrosis along with control over CNS mood, pain and appetite (15-18). Its diverse modes of use include ingestion, smoking, vaping, and topical applications, which are characterized by a broad range of frequency and dosage for both recreational and medicinal purposes. Age-related pharmacokinetic and pharmacodynamic changes can have an impact on varying withdrawal symptoms in older adults, as well as the presentation of Cannabis hyperemesis syndrome.

Psychotropic effects of Cannabis begin within minutes of inhalation, peaking at ~ 30 minutes, and taper over a period of 2-3 hours. The onset of physiological effects following oral ingestion is ~ 30-90 minutes, peaking at 2-3 hours and metabolized over the subsequent 4-12 hours (16).

The various effects are dependant on the binding of the cannabinoid receptors CB1 and CB2. The primary psychoactive ingredient in Cannabis, THC, mimics the anandamide and binds to CB1 receptors in the brain, often producing a sense of euphoria, colloquially known as a 'high.' CBD binds weakly to CB1 receptors and may interfere with the binding of THC, resulting in a lack of euphoric effect. Also, CBD has been shown to be an agonist similar to another endocannabinoid, such as anandamide, 2-arachidonoylglycerol (2-AG), and binds primarily to CB2 receptor sites. It is important to realize that the cannabinoid composition of a Cannabis plant is wide-ranging and varies by strain. Some are higher in CBD and others contain more THC.

The CB2 receptors are positioned in the immune system and nerve terminals, producing a host of defined responses, including modifying inflammatory expression by macrophages, neutrophils, B and T cell subtypes (16). The pharmacological challenge is that both CB1 and CB2 receptors influence the immune system in a challenging fashion, thus producing either agonist or antagonist effects. The endocannabinoid ligands, their transporter, receptors (CB1 and CB2) and degradative enzymes constitute the major parts of the endocannabinoid system (17,18). In addition, there are volatile components in cannabinoids which present phenolic and flavonoid patterns (18).

INFLAMMATORY BOWEL DISEASE AND IRRITABLE BOWEL SYNDROME

Cannabis has been used to ameliorate a variety of GI disorders, including abdominal pain, nausea, vomiting, diarrhea/constipation, manifestations of inflammation and dysmotility (19,20).

However, the reliability and reproducibility of clinical trials on the gastrointestinal, hepatic and

pancreatic function of medical Cannabis is problematic in that they lack standardization of cannabinoid products and there is variability in the strains studied, route of administration, influence of confounding bioactive compounds contained in the natural product, as well as the variable endpoints being measured, etc.

The ttherapeutic effect of Cannabis on the GI is based on the endocannabinoid system, which is a composite of cannabinoid receptor types, endogenous ligands (which bind the active drug to the receptors 2-AG), and the enzymes involved in cannabinoid metabolism. An important role in therapies, based on cannabinoids, is played by the potential synergy with additional components (appreciatively 60 terpenes) leading to phytocannabinoid-terpenoid entourage effects (20-22).

However, the enthusiasm to prescribe medical Cannabis for GI disorders, at the present time, should not replace approved medical therapy for treatment of any gastrointestinal, hepatic or pancreatic disease if the approved therapy is available and has not been used (22).

Cannabinoids reduce intestinal motility and secretions via CB1 agonist activity (23-32). There are observational and clinical studies reporting outcome data professing amelioration of a spectrum of GI issues such as constipation, diarrhea, anorexia, nausea, abdominal pain, providing impetus for use in motility disorders such as irritable bowel syndrome. The abdominal visceral pain of IBS is attributed to enhanced perception to colonic distention in about 70% of patients and that visceral sensation is mediated, in part, through the cannabinoid receptors (25). Efficacy was reported on abdominal pain perception, and changes in intestinal motility.

A component of this CB1 mediated the effect on motility. Gastric emptying has been demonstrated to be prolonged, leading to early satiety and may serve as a mechanism of action in a weight loss strategy, contrary to the well-known CNS mediated appetite stimulation and modifier of nausea (28, 29). The potential therapeutic role for Cannabis in diarrhea- or pain-dominant forms of IBS is supported by a small number of clinical trials (23-31).

Gastrointestinal tract has an extensive network of CB2 receptors that may promote integrity of intestinal epithelium (32) and mediate significant mucosal anti-inflammatory effects (33). Cannabidiol receptor agonists were demonstrated to have a significant effect on the GI mucosal immune inflammatory cascade *in vitro* (33) and *in vivo* (34).

Storr et al. reviewed the involvement of the endocannabinoid system in the context of symptoms associated with inflammatory disease (35). The authors showed that activation of CB1 and CB2 receptors decreases hypersensitivity in the gut. They also explained the role of this system in the pathophysiology of inflammation, as well as the possible therapeutic intervention using Cannabis (35). Interestingly, there may be a difference in response between patients with ulcerative colitis (UC) and CD, as Storr and his colleagues reported worse outcomes in CD patients receiving CBD compared with the UC group (35).

CBD has been shown to improve both inflammatory signs and symptoms of IBD. CBD purportedly exerts an anti-inflammatory effect by stimulating the peroxisome proliferator activated receptor gamma (PPAR-gamma) (36). In a prospective cohort survey study, Allegretti et al. (37) reported that the majority of their IBD patients found Cannabis to be very helpful in completely relieving abdominal pain, nausea and diarrhea when taken in conjunction with their prescription anti-inflammatory medications.

Objective parameters of clinical, laboratory, endoscopic improvement in Crohn's Disease (CD) patients have been described and demonstrated by a group of Israeli gastroenterologists (38-41). Their studies using medical Cannabis show a reduction of the CD inflammatory index with no adverse events. Unfortunately, there was not a total remission of the disease. The authors also discuss the implications of its use with emphasis on bioavailability and the carry-over period, which are important factors for monitoring the patients and specific diagnosis. The requirement to establish the specific dose cannabinoids, are also explained, as well as appropriate medical conditions, optimal dose, and mode of administration in order to obtain the beneficial effects. The authors note that it is important to avoid any harmful effects of cannabinoid use, especially addiction (38-41).

The same group initiated a clinical trial employing twenty patients with a Crohn's disease activity index (CDAI) >200 that were randomized to receive oral (10 mg) CBD or placebo twice daily for 8 weeks. The average CDAI before cannabidiol consumption was 337±108 and 308±96 (p=NS) in the CBD and placebo groups, respectively.

After treatment, the CDAI was 220±122 and 216±121 in the CBD and placebo groups. CBD was safe but had no beneficial effects (40). In an additional placebo-controlled study in 21 chronic CD patients

using a higher dose of CBD, there was a decrease in the CD activity index >100 in 10 out of 11 (90%; from 330 ± 105 to 152 ± 109) in subjects taking Cannabis, compared to 4 out of 10 (40%; from 373 ± 94 to 306 ± 143; P = .028) individuals taking placebo. Complete remission (CDAI score, <150) was achieved in 5 out of 11 subjects in the Cannabis-treated individuals (45%) and 1 out of 10 in the patients receiving placebo (10%; P = .43). Importantly, 3 individuals receiving medical Cannabis that were previously steroid-dependant became steroid-free. (41)

Kafil et al. (42) reviewed available publications on Cannabis safety and efficacy in adults with active ulcerative colitis. A non-statistical trend for efficacy without signals of adverse clinical outcomes was reported. A study on prevalence and patterns of marijuana use in young adults with inflammatory bowel disease emphasizes the need to survey the way these individuals use the plant and the different implications of the mode of self-administration (43).

An additional study by Coi et al. (45) summarizes an analysis of the Agency for Healthcare Research and Quality's 2016 Nationwide Re-admissions Database. The team identified 6,798 adult patients with IBS of whom 357 were Cannabis users who participated at the study. The inclusion criterion was a principal diagnosis of IBS using ICD-10 CM codes. The primary outcome was a 30-day readmission to hospital. For Cannabis-consuming patients the mean age was 36.7 (range 34.5-38.9) years and 53.3 (52.6-54.1) years, respectively. Women accounted for 62% and 81% of the two groups. In their cohort study of hospitalized IBS individuals, the authors found that all-cause 30-day readmission rates were 12.7% in non-Cannabis users and 8.1% in Cannabis users. After adjustment for age, sex, median income by zip code, insurance status, Charlson Comorbidity Index, hospital bed size, teaching status, and location, the adjusted odds ratio in Cannabis users was 0.53 (95% CI 0.28-0.99). Also, Cannabis use appeared to correlate with shorter hospital stays leading to lower total hospitalization charges. Cannabis use was also associated with a slightly higher survival rate compared with non-users (45).

An additional study compared the prevalence of UC- related complications among Cannabis users and non-users hospitalized with a primary diagnosis of UC. Using data from the Healthcare Cost and Utilization Project- National Inpatient Sample during the period 2010-2014, the authors identified a total of 298 Cannabis users with the same diagnosis. The prevalence of partial or total colectomy was lower in Cannabis users compared to non-users (4.4% vs 9.7%, P=.010). Moreover, there was a non-significant trend toward a lower prevalence of bowel obstruction (6.4% vs 10.7%, P=.057). Also, Cannabis users had shorter hospital length-of-stay (4.5 vs 5.7days P<.007) compared to non-users (46).

A similar approach was taken by another research team which studied the impact of recreational marijuana usage on in-hospital outcomes. The outcomes of CD as well as UC was assessed using the Nationwide Inpatient Sample datasets (2010-2014). This study linked the complications of adults with CD and UC hospitalizations with Cannabis use (47). They followed a cohort of 6,002 CD patients: (2,999 Cannabis users and 3,003 controls) and 1,481 UC patients (742 Cannabis users and 739 non-users). The prevalence of colorectal cancer was 0.3% in CD individuals that use Cannabis while in CD patients that do not use Cannabis the prevalence of colorectal cancer was 1.2%, (P<0.001). Additionally, the need for parenteral nutrition was 3.0% in Cannabis users vs. 4.7% in non-users, (P=0.001). Also, the co-morbidity of anemia was observed in 25.6% of Cannabis users vs. 30.1% in non-users (P<0.001). On the contrary, in the Cannabis-user cohort there were more active fistulizing disease or intra-abdominal abscesses (8.6%) vs. the same complications (5.9%), (P<0.001) when compared with non-users.

In patients with UC a relatively lower frequency of post-operative infections (<11 vs. 3.4%, P=0.010) was observed. Both the CD as well as the UC-Cannabis patients had shorter mean hospital stays (4.3 vs. 5.7 days, P<0.001) (47).

Reviewing some of the risks and benefits in clinical management on IBD utilizing Cannabis, Swaminath et al. concluded that the patients benefited in controlling symptoms and improving quality of life. However, true disease modification and improvement in biomarker profiles or endoscopic healing was not observed (48).

The treatment of IBD frequently requires immunosuppressive and biologic therapies, which carry an increased risk of infections and possible malignancy. There is a continued search for safer and more natural therapies in the treatment of IBD. As a result, medical Cannabis therapy may be considered an alternative adjunct to conventional therapeutics in the management of the signs and symptoms of active IBD, but not as primary anti-inflammatory therapy. It is important to understand the need to study the inflammation and repair of intestinal mucosa under the influence of Cannabis.

Di Sabatino and colleagues described modulation of the ECS using endoscopic biopsy specimens from 41 patients with CD and 33 patients with UC. The biopsies were analyzed for endocannabinoid levels, expression of cannabinoid receptors, and activity of enzymes involved in endocannabinoid synthesis and degradation. The levels of anandamide were significantly decreased in inflamed IBD mucosa. These levels correlated with a decrease in expression of N-acyl-phosphatidyl-ethanolamine-phospholipase D (NAPE-PLD) and an increase in expression of fatty acid amide hydrolase (FAAH). The CB1 expression in these biopsies (CD and UC) were increased when compared with the biopsies from a non-inflammed intestine. Interestingly, CB2 levels in the same biopsies did not change (49).

The Canadian Association of Gastroenterology published guidelines for use of Cannabis in gastroenterological and hepatic disorders (50). These guidelines are important since many individuals are prone to use cannabis and cannabis-containing products at no restrictions.

HEPATOLOGY

Cannabinoids influence a variety of liver disorders, including hepatic steatosis and fibrosis, portosystemic encephalopathy, alcoholic liver disease (ALD) (18). Stimulation of CB1 receptors in the liver may promote steatosis via increasing lipogenesis, decreasing fatty acid oxidation and inducing hyperphagia; whereas, CB1 antagonists suppresses hepatic steatosis (18). Hepatic CB1 receptors also may stimulate fibrogenesis especially in alcohol hepatitis, and that in-vitro and in-vitro studies showed that CB1 antagonists may protect against development of alcohol induced liver fibrosis (51).

Daily cannabis use in viral hepatitis patients is controversial. Ishida et al. (52) found daily cannabis use to be strongly associated with moderate to severe fibrosis in chronic viral hepatitis C (HCV) patients. Brunet et al. (53) and Liu et al. (54) described no adverse effects of cannabis use on the natural history of HCV. There are no reported data on the impact of cannabis on the natural history of viral hepatitis B (HBV) infection. In patients co-infected with human immunodeficiency virus (HIV) and HCV, cannabis use may reduce the rate of steatosis (55) as well as insulin resistance (56). However, the impact on fibrogenesis in the co infected group is controversial and it is not recommended.

Stimulation of CB2 receptors, which may be upregulated in chronic liver disease (57) have been reported to protect against hepatic fibrosis (58). Curiously, in ALD, the balance of cannabinoids may have a potential protective effect by reducing oxidative stress that leads to inflammation and steatosis (59) thereby resulting in lower rates of alcohol-induced steato-hepatitis, and cirrhosis (60).

Epidemiological studies suggest that cannabis use was associated with a lower prevalence of non-alcohol fatty liver disease (61). Cannabis hepatotoxicity is arguable, but cannabinoids may have a defined role management of chronic liver disease as more studies emerge.

Vázquez-Bourgon et al. Cannabis consumption and non-alcoholic fatty liver disease for three years in first episode non-affective psychosis patients. They assessed the potential therapeutic target in the management of Nonalcoholic fatty liver disease (NAFLD) the clinical outcomes and in-patient in 390 NAFLD patients (62). The patients were evaluated at baseline and after 3 years of initiating the antipsychotic treatment. Only 6.7% of patients were taking Cannabis at entry in the study as they self-reported their cannabis. Liver steatosis and fibrosis were evaluated through validated clinical scores Fatty Liver Index (inflammation) and fibrosis. At 3-year follow-up, cannabis users presented significantly lower inflammation scores than non-users ($F = 13.874$; $p < .001$). Moreover, patients maintaining Cannabis consumption after 3 years presented the smallest increment in inflammation over time, which was significantly smaller than the increment in FLI presented by individuals that discontinued Cannabis ($p = .022$) and individuals that never-used Cannabis ($p = .016$). No differences were seen in fibrosis scores associated with Cannabis.

PANCREAS

Canabinoids have a significant impact on the endocrine system, including the activity of the pituitary gland, adrenal cortex, thyroid gland, pancreas, and gonads (63). Acute pancreatitis has been diagnosed in an individual (64). Alcohol in combination with Cannabis induced pancreatitis has been reported in a female that was consuming Cannabis daily for three years (65).

The team of Njei (66) aimed to investigate the impact of Cannabis on post-endoscopic retrograde cholangio-pancreatography pancreatitis. Employing the US Nationwide Inpatient Sample to identify patients who underwent endoscopic retrograde cholangio-pancreatography pancreatitis from 2004 to 2014, The authors demonstrated cannabis was

associated with increased risk of pancreatitis (IRR, 1.70; 95% confidence interval [CI], 1.50-1.90; P < 0.01) (66).

In a systematic review, the classification criteria Cannabis-induced acute pancreatitis was defined by preceding use of cannabis and exclusion of common causes of acute pancreatitis when reported (67). From 2004 to 2016. there were 26 cases of cannabis-induced acute pancreatitis (23/26 men; 24/26 under the age of 35 y). Acute pancreatitis correlated with increased cannabis use in 18 patients. Recurrent acute pancreatitis related temporally to cannabis use was reported in 15 of 26. There are 13 reports of no further acute pancreatitis episodes after cannabis cessation (67).

CANNABIS USE IN GASTROINTESTINAL SYMPTOMS:

Nausea and Vomiting:

Cannabis and related cannabinoids may be considered as primary or adjunctive therapy for limited prescription periods for management of refractory nausea and vomiting associated with chemotherapy, abdominal pain in both benign and malignant disease states, especially where conventional therapeutics have been ineffective (68).

CB1 receptors are distributed throughout the brain, including dorsal vagal complex of the brain which is involved in pathogenesis of vomiting (69). A meta-analysis by Smith et al. (70) concluded that cannabinoids yielded significant efficacy in the treatment of chemotherapy induced nausea and vomiting.

Anorexia and weight loss:

CB1 receptors in the hypothalamus contribute to the regulation of appetite and energy balance. Studies on efficacy of exogenous cannabinoids in modifying appetite and weight gain are controversial and may reflect differences in study design, disease state being evaluated and outcome parameters. Strasser et al. (71) reported no benefit from synthetic cannabinoids in malignant anorexia-cahcexia compared to placebo controls; whereas, Brisbois et al. (72) demonstrated significant improvement in appetite, enhancement of taste, and increased protein-calorie intake in cannabinoid treated cancer patients vs placebo treated control group.

Patients with AIDS associated anorexia and weight loss have had significant improvement in weight gain and quality of life (73); however, Whiting et al. (68) could not reproduce these data and suggest that there is limited evidence of an association between cannabinoid use and weight gain, enhanced appetite and increase in body fat.

Paradoxically, cannabinoids may have a therapeutic role in weight reduction strategies. Alshaarowy and Anthony (74) recently showed an inverse relationship between cannabis use and obesity. The proposed mechanism of action is that chronic cannabis use may down regulate CB1 receptors and upregulate CB2 receptors in the hypothalamus leading to weight reduction.

Cannabinoid hyperemesis syndrome (CHS)

Paradoxical pernicious protracted nausea and vomiting syndrome has emerged with increasing rates of regular cannabis use, coined “Cannabis Hyperemesis Syndrome” previously called Cyclical Vomiting Syndrome (75). This syndrome arises exclusively in patients who indulge in chronic cannabis smoking (daily for years), and not in patients who only indulge in oral cannabis ingestion (76). Low dose CBD yields anti-emetic properties and higher doses produce a proemetic effect (77). There are 3 phases in clinical course of CHS: prodromal, hyperemetic, recovery.

Prodromal phase: early morning nausea, fear of vomiting and non-specific abdominal discomfort that may last for months to years;

Hyperemetic phase: development of intense nausea, pernicious vomiting and diffuse abdominal pain prompting the afflicted to be assessed in an emergency department. There is a unique need in this phase for afflicted patients to take numerous, long hot showers or baths in an attempt to alleviate this reaction. Compulsive hat bathing may increase blood flow to the skin to dissipate elevated core body heat which is believed to be due to cannabis induced rise in core body temperature with paradoxical decrease in skin temperature (78). Patients may propagate this phase by continuing to consume cannabis for the misbelieve that they need the antiemetic property of the drug (79). Treatment recommendations in addition to cannabis withdrawal in this phase include haloperidol i.v. infusion and topical capsaicin cream (79).

Recovery phase: highlighted by improving symptoms and signs described above, weeks to months after withdrawing from cannabis consumption, with progressive weight regain as a result of a return to normal mood and eating patterns (79).

A case report presents a chronic cannabis smoker who developed severe Barrett's esophagus. A 41-year-old African American male presented with an exacerbation of nausea and vomiting. The patient reported that he smoked cannabis two to three times daily for the past 20 years. Upper endoscopy and histology displayed long-segment Barrett's esophagus indefinite for dysplasia (80). With the increase in the prevalence of cannabis smoking, endoscopic surveillance guidelines may need to be modified to include younger (81),

Recommendations for cannabis withdrawal are growing, while counseling techniques are evolving to promote effective management of patients afflicted with psychological and physical adverse effects of chronic cannabis use (79 - 82).

RISKS OF LONG-TERM TREATMENT WITH CANNABIS/ CANNABINOIDS IN IBD

IBD treatment with Cannabis in adolescents is not recommended. Use of Cannabis has shown neurological changes in adolescents, including a decrease in gray matter volume in certain brain areas. This aspect requires attention since only few patients have knowledge of possible adverse effects (50, 80-83).

Many of the psychotropic effects of Cannabis are seen in centrally acting cannabinoids, namely THC. Adverse effects of acute use include anxiety, panic, psychosis, tachycardia and increased appetite with dry mouth. Long-term use leads to dependence, tolerance, and withdrawal upon discontinuation. Symptoms of withdrawal include increased irritability, sleep disturbance, anorexia, and depression. However, only approximately 10% of Cannabis users ever develop dependency, which is comparatively less than what is seen in tobacco, alcohol, cocaine, or heroin use. No deaths have been solely attributed to marijuana use. Crohn's disease is influenced by age (84) and possible co-morbidities that appear with more medication and less vital sources. Long-term use of Cannabis effects brain structure (85). It may also produce important substance-use disorders in the elderly (86).

As a response to the legalization of Cannabis, and its misuse, the Canadian Coalition for Seniors' Mental Health published "Canadian Guidelines on Cannabis Use Disorder Among Older Adults (86)." Prescribing medical Cannabis for IBD or IBS requires an understanding of Cannabis use disorders in the general population and the need to treat them utilizing psychosocial and pharmacological interventions (86). Barriers to authorizing medical Cannabis include the lack of familiarity around its dosing and safety. Professional organizations such as the Canadian Psychiatric Association, American Academy of Pediatrics and Canadian Pediatric Association (86-89) have published warning on the lack of data on efficacy and safety of medical Cannabis in the pediatric population. The Canadian Pediatric Society asked policymakers and physicians to limit pediatric access to medical Cannabis until further evidence becomes available since the efficacy or safety of Cannabis use for any indications in children is not shown. Moreover, self-medicate interventions with Cannabis can also be harmful (90).

CONCLUSION

The principles of pharmacotherapy, namely studying the efficacy and safety of a therapeutic agent and understanding the risk: benefit ratio of a medication and the disease for which the medication is being prescribed, applies to Cannabis as it does to any drug. Therefore, rigorous clinical trials need to be designed and undertaken to answer the clinical questions of appropriate indications for medical cannabis, therapeutic dosing and appropriate monitoring for effectiveness and adverse effects. These principles are being applied for promising use of cannabis in gastrointestinal/hepatico-pancreatic disorders and diseases, and as more well-designed clinical research trials are being conducted, rational prescribing profiles will be provided.

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