The Effects and Benefits of Cannabis on the Gastrointestinal Disorders

8

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Introduction

The endocannabinoid system plays an important role in the homeostasis and cellular function of the gastrointestinal (GI) tract [1]. Both cannabinoid receptors, CB_1 and CB_2 are present in the enteric nervous system and are specifically tied to cholinergic neurons. Additional receptors are also seen in the colonic epithelial cells and vascular smooth muscle cells of the colon. Given the vast distribution of these receptors in the GI tract and potential effects on activation, cannabinoids can have a multitude of effects including include nausea/vomiting, pain regulation, motility and regulation of inflammation. While several GI organizations have not fully approved the use of cannabis for any gastrointestinal, hepatologic or pancreatic diseases, new research is showing promise for specific conditions.

The GI Tract and Endocannabinoid System (See Chap. 3 on Pharmacology of Cannabinoids)

- The two main endocannabinoid receptors in the GI tract are CB_1 and CB_2 [1–3].
  - Type 1 (CB_1) receptors are located in the enteric nervous system (such as the epithelium of the GI tract) and sensory terminals of vagal and spinal neurons, regulating neurotransmitter release.
    CB_1 receptors are also seen in the smooth muscle cells of the colon.
  - Type 2 (CB_2) receptors are mostly distributed through the immune system producing a host of immunotherapeutic responses, including modifying inflammatory expression by macrophages, neutrophils, B and T cell subtypes.

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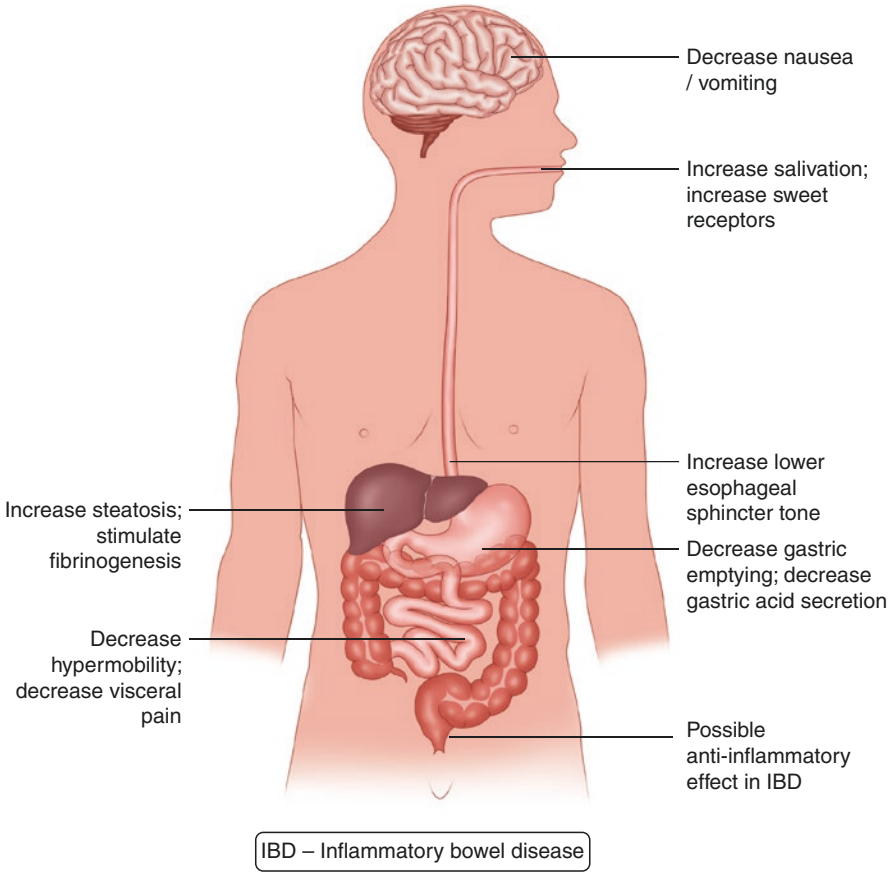

Fig. 8.1 Effects of cannabis on the gastrointestinal tract

- The GI tract can produce and metabolize its own ligands (Anandamide and 2-Arachidonoylglyerol) and as well as up- and down- regulate endocannabinoid receptors in order to facilitate appropriate bowel function [1].
- Effects on the GI tract include [3]: See Fig. 8.1.
  - Decrease in esophageal lower sphincter relaxation. This reduces emesis and provides antiemetic properties.
  - Decrease gastric acid secretion and gastric emptying.
  - Reduces hypermotility of the bowels associated with inflammatory diseases. This may potentially benefit diarrhea and other inflammatory aspects of inflammatory bowel disease.

  - Decrease visceral pain. (See Chap. 11 on The use of Cannabis for pain management)
- Both CB_1 and CB_2 receptors inhibit GI muscle contraction through presynaptic decrease in excitatory neurotransmitter (acetylcholine and Substance P) release.

Effects of Cannabis on Specific GI Conditions

1: Anorexia and Weight Loss

- CB_1 receptors in the hypothalamus contribute to the regulation of appetite and energy balance.
- Studies on the efficacy of exogenous cannabinoids in modifying appetite and weight gain are controversial and may reflect differences in study design, the specific disease state being evaluated, and outcome parameters.
  - Strasser et al. reported no benefit from synthetic cannabinoids in malignant anorexia-cachexia compared to placebo controls; whereas, Brisbois et al. demonstrated significant improvement in appetite, enhancement of taste, and increased protein-calorie intake in cannabinoid treated cancer patients versus placebo treated control group [4, 5].
- Patients with AIDS associated anorexia and weight loss have had significant improvement in weight gain and quality of life with the use of cannabis [6].
- Cannabinoids may have also have a therapeutic role in weight reduction strategies.
  - Alshaarowy and Anthony recently showed an inverse relationship between cannabis use and obesity [7].

    The proposed mechanism of action is that chronic cannabis use may down regulate CB_1 receptors and upregulate CB_2 receptors in the hypothalamus leading to weight reduction.

2: Nausea/Vomiting

- Cannabis and related cannabinoids may be considered as primary or adjunctive therapy for limited periods in the management of refractory nausea and vomiting associated with chemotherapy, especially where conventional medications have been ineffective [8].
- CB_1 receptors are distributed throughout the brain, including the dorsal vagal complex of the brainstem (area postrema) which is involved in pathogenesis of vomiting [9].
  - A meta-analysis by Smith et al. concluded that cannabinoids yielded significant efficacy in the treatment of chemotherapy induced nausea and vomiting (CINV) [10].

- Despite evidence of its usefulness, the American and European oncology guidelines do not recommend cannabis be used as a first line agent in the management of CINV. Instead, they state that cannabinoids should be prescribed for CINV after conventional medical therapy has failed [11].
- The long-term effectiveness and safety of cannabis for chronic gastrointestinal symptoms, such as Irritable Bowel Syndrome and nausea/vomiting, remain unknown.
  - Until further studies of cannabis in the management of nonspecific GI symptoms should be avoided

3: Irritable Bowel Syndrome (IBS)

- The prevalence of IBS varies from 15 to 40% worldwide. Given the high prevalence and limited therapeutic options to manage the symptoms of IBS, cannabis offers an alternative therapeutic option.
- Cannabinoids reduce intestinal motility and secretions via CB_1 agonist activity [12].
- There are anecdotal and clinical studies reporting improved symptoms for a spectrum of GI issues such as IBS-constipation, diarrhea, anorexia, nausea, abdominal pain, providing impetus for use in motility disorders such as irritable bowel syndrome [13–16].
- 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 [14].
  - Given the role of the cannabinoid receptor in IBS would suggest that cannabis may benefit these patients.
- The potential therapeutic role for cannabis in diarrhea- or pain-dominant forms of IBS is supported by small number of clinical trials.
  - Arguable efficacy was reported on abdominal pain perception, and changes in intestinal motility.
- A component of this CB_1 mediated effect on motility and prolonged gastric emptying has been shown to cause early satiety.
  - This has been suggested as a method of weight loss strategy, contrary to the well-known CNS mediated appetite stimulation and modifier of nausea.

4: Inflammatory Bowel Disease (IBD)

- The incidence of IBS varies by geography. It is estimated that 0.7% of Canadians and 1.3% of adults in the United States suffer from IBS.
  - The incidence is higher in Northern Europe and those with a family history.
- The pathophysiology is complicated, and both, a genetic predisposition as well as environmental factors contribute to the risk of having IBD.

- The pathophysiology of IBD is a complex interplay between:
  - Epithelial cells.
  - Immune cells—activation and uncontrolled inflammation within the bowel that is linked to unregulated T-cell activation.
  - Normal microbial flora—patients with IBD have a different composition of gut microbes which can modify the inherent epithelial cells.
- The two main forms of inflammatory bowel disease (IBD) are Crohn's Disease and Ulcerative Colitis. Both conditions have been linked to altered immune system responses.
  - Ulcerative Colitis (UC)

    UC is a chronic inflammatory process that extends from rectum proximally to cecum, and is limited to the colo-rectal mucosa in a confluent pattern.

    The inflammation is limited to the mucosal and superficial submucosal layers.

    The mucosa is granular, friable and ulcerated with edema, hemorrhage, with evolution of pseudo-polyps (inflammatory polyps) over time.
  - Crohn's Disease

    Crohn's Disease can affect any part of the gastrointestinal tract and usually spares the rectum.

    Crohn's Disease affects all the layers of the GI tract, with transmural inflammation that may be complicated by abscess and fistulae formation, featured by "cobble stoning" pattern of mucosal inflammation and deep serpiginous ulceration.

    Focal crypts and abscesses are seen on microscopy.
- Non-GI manifestations of IBD include:
  - Dermatologic—erythema nodosum and pyoderma gangrenosum.
  - Musculoskeletal—arthritis, ankylosing spondylitis, sacroiliitis.
  - Ophthalmic—uveitis, iritis, episcleritis.
  - Hepatobiliary—primary sclerosing cholangitis (PSC)
- The gastrointestinal tract has an extensive network of CB_2 receptors that may promote the integrity of intestinal epithelium. They potentially mediate significant mucosal anti-inflammatory effects, which are known to be predisposing factors in IBD [17, 18].
- Cannabidiol (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) [19].

    A prospective cohort study reported that the majority of their IBD patients found cannabis to be very helpful in completely relieving abdominal pain, nausea and diarrhea taken in conjunction with their prescription anti-inflammatory medications [20].

    Objective parameters of clinical, laboratory, and endoscopic improvement in IBD (Crohn's Disease) patients have been described and demonstrated [21, 22].

Interestingly, there may be a difference in response between patients with UC and Crohn's Disease.
    - There may be worse outcome in Crohn's Disease patients receiving CBD compared to the UC group [23].
- 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 [24]
- To date there is insufficient evidence for cannabis to be effective to alter the course of disease in patients with inflammatory bowel disease. Further studies are needed to provide evidence on the role of cannabis on the natural history of IBD [25]

5: Liver Diseases

- There is a growing body of evidence to suggest that cannabinoids influence a variety of liver disorders, including hepatic steatosis and fibrosis, portosystemic encephalopathy, and alcoholic liver disease [24].
- Stimulation of CB_1 receptors in the liver may promote steatosis via increasing lipogenesis, decreasing fatty acid oxidation and inducing hyperphagia. On the other hand, CB_1 antagonists suppresses hepatic steatosis [25].
  – Hepatic CB_1 receptors may also stimulate fibrogenesis especially in alcohol hepatitis, and in-vitro and in-vitro studies showed that CB_1 antagonists may protect against development of alcohol induced liver fibrosis [26].
- The effects of daily cannabis use in viral hepatitis patients is controversial.
  – Ishida et al. found daily cannabis use to be strongly associated with moderate to severe fibrosis in hepatitis C patients [27].
  – Brunet et al. and Liu et al. discovered no adverse effects of cannabis use on the natural history of Hepatitis C Virus (HCV) [28].
  – There are no reported data on the impact of cannabis on the natural history of Hepatitis B infection.
  – In patients co-infected with HIV and Hepatitis C, cannabis use may reduce the rate of steatosis as well as insulin resistance. The impact on fibrogenesis in the co-infected group is controversial [29, 30].
- Stimulation of CB_2 receptors, which may be upregulated in chronic liver disease, have been reported to protect against hepatic fibrosis.
- Interestingly, in alcoholic liver disease, the balance of cannabinoids may have a protective effect by reducing oxidative stress that leads to inflammation and steatosis thereby resulting in lower rates of alcohol steato-hepatitis, cirrhosis and hepatocellular carcinoma.
- Epidemiological studies suggest that cannabis use is associated with a lower prevalence of non-alcohol fatty liver disease.
- While cannabis hepatotoxicity is arguable, cannabinoids may have a defined role in the management of chronic liver disease as more studies emerge.

6: Pancreatitis

- The pancreas contains both CB_1 and CB_2 receptors.
  - As in liver, activation of CB_1 pancreatic receptors promotes fibrogenesis, opposed by CB_2 receptor agonists.
- Cannabis induced pancreatitis has been reported and may be dose and duration of use dependent.
  - Treatment is the same as other causes of medical pancreatitis.

7: Cannabinoid Hyperemesis Syndrome (CHS) (See Chap. 12 for More Details on Management and Treatment)

- There is an increased incidence of CHS seen in the emergency department. The prevalence is difficult to determine given the variability in symptoms and use of cannabis, as well as underreporting of this condition.
- CHS is most commonly seen in patients regularly use cannabis. It presents with protracted nausea and vomiting.
- While low dose CBD yields anti-emetic properties, higher doses have a pro-emetic effect. Hence the reason why it is seen commonly in chronic users.
- The clinical course follows three phases:
  - ***Prodromal phase***: This phase presents with early morning nausea, fear of vomiting and non-specific abdominal discomfort. The prodromal phase can last for months or years.
  - ***Hyperemetic phase***: This phase begins with the development of intense nausea, pernicious vomiting and diffuse abdominal pain. This is when patients present to the Emergency Department as they cannot control their vomiting with typical anti-emetic agents.

    Patients may propagate this phase by continuing to consume cannabis for the misbelief that they need the antiemetic property of the drug.

    See section in Chap. 12 on specific treatment for CHS in the Emergency Department.
  - ***Recovery phase***: This phase is 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.

Conclusion

- The principles of pharmacotherapy, understanding the risk:benefit ratio, and the efficacy of a compound towards a disease 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 uses of cannabis in gastrointestinal, hepatic, and pancreatic disorders.
  - As more well designed clinical research trials are being conducted, rational prescribing profiles will be available.
- The Canadian Association of Gastroenterology recommends "that physicians in Canada familiarize themselves with important aspects of medical cannabis before authorizing a patient for medical use. Moreover, with recreational use being so common, it also behooves physicians to understand the risks involved for patients and to be able to counsel them accordingly" [31].
- A comprehensive summary of the role of cannabis in gastrointestinal, hepatic and pancreatic diseases, and effects on metabolic disorders such as obesity, have been published by Gotfried et al. [32].

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