

Richard W. McCallum, MD, FACP, FRACP (Aust), FACG

## Cannabis in Gastrointestinal Disorders



Mohammad Bashashati



Richard W. McCallum

For thousands of years, cannabis and its derivatives have been used for the treatment of human diseases including those that present with gastrointestinal (GI) symptoms. Within the past decades and after the discovery of the endocannabinoid system in the body, largely anecdotal rather than scientific reports on the effects of cannabis in human diseases began to appear and resulted in clinicians becoming more interested in prescribing synthetic or herbal cannabinoids for their patients. Moreover, based on the media and advertisements as well as their personal experience, patients and particularly those with debilitating diseases such as cancer and chronic disorders with abdominal pain such as inflammatory bowel disease showed interest in smoking cannabis. Despite the strong evidence supporting the therapeutic role of cannabis in nausea and vomiting related to chemotherapy and cachexia of AIDS, studies on the use of cannabis for other GI disorders are limited and sparse. In this article, we review available clinical evidence in supporting medical cannabis for GI diseases.

### INTRODUCTION

With over 5000 years of use, cannabis or marijuana, i.e. dried leaves, stems, flowers, and seeds of the plant *Cannabis sativa* and its compressed resin form, i.e. hashish are the most common consumed illicit drugs worldwide and in the United States.<sup>1,2</sup>

The chemical derivatives of *Cannabis sativa* are called “phytocannabinoids”, while there are also synthetic cannabinoids which have cannabinomimetic effects.<sup>3</sup>

Besides being used recreationally, cannabis and its derivatives have been valuable for the treatment of human diseases for centuries. The term “medical cannabis” or “medical marijuana” describes medicinal use of cannabis or cannabinoids.<sup>4</sup> However, based on their potential for being abused, it is very important to define a border between medical and recreational cannabis.<sup>5</sup>

Under federal law of the United States, cannabis is a Schedule I substance and its use is illegal; however, the District of Columbia and 23 states have legalized medical cannabis. Moreover, in some states recreational use of marijuana is legal and possession of limited amounts of marijuana has been decriminalized. Medical cannabis is approved for chronic, debilitating and long-lasting disorders such as cancer, AIDS and multiple sclerosis and occasionally, this is legally allowed for

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Mohammad Bashashati, MD<sup>1</sup> Richard W. McCallum, MD<sup>2</sup>  
<sup>1</sup>Research Associate, Snyder Institute for Chronic Diseases and Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada <sup>2</sup>Professor and Founding Chair, Department of Internal Medicine, Texas Tech University Health Sciences Center, El Paso, TX

gastrointestinal (GI) patients with Hepatitis C, Crohn's disease, nausea and cachexia.<sup>6</sup>

Due to the legalization of medical cannabis in several states, physicians who see patients with GI diseases may need to prescribe cannabis. Alternatively, they might be asked about the benefits and adverse effects of medical marijuana. In addition, due to decriminalization of cannabis in some states, a practicing physician may see more patients who use cannabis recreationally. Therefore, it is important for a physician to know the therapeutic potentials of cannabis and its natural or synthetic derivatives and the possible adverse effects of cannabis use.

This article highlights the benefits of medical cannabis in GI diseases and discusses possible side effects of medical cannabis and cannabis intoxication.

## Cannabis and Cannabinoids

$\Delta$ 9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are two major components of cannabis. While THC has psychoactive effects, CBD is devoid of central side effects.<sup>7</sup> For medicinal purposes, cannabis can be smoked or vaporized or its extracts/juice can be used orally; however, if taken orally, its absorption is slow and its therapeutic components are less bio-available. More reliable forms of medicinal cannabis in terms of dosage are synthetic compounds which are structurally related to THC, e.g. Nabilone (Cesamet) and Dronabinol (Marinol), as well as accurately measured mixture of THC and CBD extracted from the cannabis plant, e.g. Nabiximols (Sativex). Nabilone and Dronabinol are used orally; however, Nabiximols is an oromucosal spray.<sup>8</sup> Besides these, there are synthetic cannabinoid agonists which have not yet been used in the clinic, but have shown significant therapeutic potential in pre-clinical studies as well as the potential for being abused.<sup>9</sup>

The discovery of endocannabinoid system in 1990s shed light into our understanding of the mechanisms of cannabis function in the body. Moreover, it introduced new potential therapeutic strategies through modulating endocannabinoid system.<sup>10</sup> Such an approach is still under clinical evaluation for different clinical conditions and hopefully their results will be released in the early future.

## Endocannabinoid System

Basically, our body has endogenous cannabinoids, which are present both in periphery and the central nervous

system (CNS). Two main endogenous cannabinoids are anandamide (AEA) and 2-arachydonilglycerol (2-AG). AEA and 2-AG are synthesized on demand from the membrane phospholipids and activate presynaptic cannabinoid receptors 1 and 2 (CB<sub>1</sub> and CB<sub>2</sub>). Endogenous cannabinoids, the enzymes that are involved in the biosynthesis and degradation of them besides CB<sub>1</sub> and CB<sub>2</sub> receptors are the components of the "endocannabinoid system".<sup>11,12</sup>

N-arachidonoylphosphatidylethanolamine phospholipase D (NAPE-PLD) and diacylglycerol lipase (DAGL) are the major enzymes in the biosynthesis of AEA and 2-AG, respectively. On the other hand, AEA is degraded by fatty acid amide hydrolase (FAAH), while monoacylglycerol lipase (MAGL) hydrolyses 2-AG. In addition to these, cyclooxygenase 2 (COX-2) is an important enzyme which metabolizes both AEA and 2-AG and produces prostaglandins.<sup>11-13</sup>

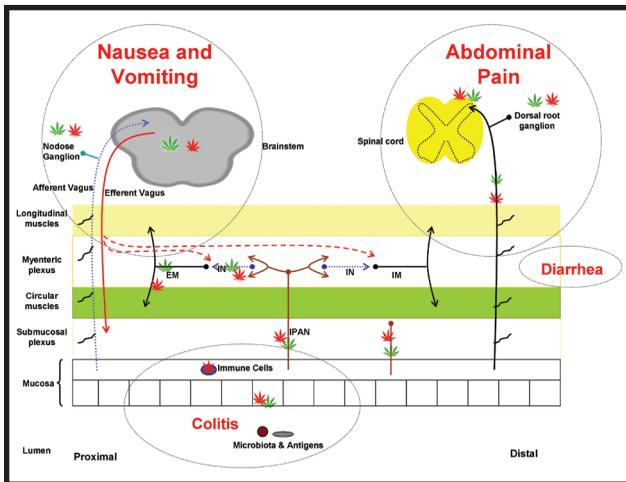
As mentioned, AEA and 2-AG activate CB<sub>1</sub> and CB<sub>2</sub> receptors. Another potential receptor for AEA is the transient receptor potential vanilloid type-1 (TRPV1). CB<sub>1</sub> and, to some extent, CB<sub>2</sub> receptors are present in the central and enteric nervous system. On the other hand, CB<sub>2</sub> receptors are more abundant on immune cells, making them a good drug target during inflammation. Despite their variable distribution in different organs, the function of CB<sub>1</sub> and CB<sub>2</sub> receptors are not distinct and both can either regulate neuronal signaling or might be involved in immune mediated mechanisms.<sup>12,14</sup>

Endocannabinoid system is present in the GI tract. Although its components have been observed in almost all layers of intestinal sections, they are majorly localized to the enteric nervous system including the myenteric and submucosal plexi. Moreover, there is some evidence to support the presence of CB<sub>1</sub> and CB<sub>2</sub> receptors on the epithelial cells.<sup>10,12</sup> The localization of CB<sub>1</sub> and CB<sub>2</sub> receptors potentially defines the pharmacophysiology of cannabis and cannabinoids in the GI tract making them a potential target for the treatment of GI disorders such as abdominal pain, diarrhea, nausea and vomiting as well as GI inflammation.

Figure 1 shows the distribution of cannabinoid receptors in the GI tract and CNS regions that control GI function.

## The Physiology of Endocannabinoid System in the GI Tract

Our understanding of the physiology of cannabinoids and endocannabinoids relies heavily on findings from



**Figure 1.** The distribution of cannabinoid receptors in the gastrointestinal (GI) tract and central nervous regions that regulate GI function. CB<sub>1</sub> receptors (green leaf) and CB<sub>2</sub> receptors (red leaf) are present on the enteric neurons, GI mucosa, brainstem and viscerosensory pathways. Immune cells express CB<sub>2</sub> receptors and besides mucosal cannabinoid receptors may control colitis/inflammation. The cannabinoid receptors regulate GI motility through their presence on the intrinsic primary afferent neurons and interneurons that are connected to excitatory motor neurons. Through their presence in the vomiting centers of the brainstem and the vagal pathway, activated cannabinoid receptors inhibit vomiting and because of their presence on the viscerosensory neurons and dorsal horn of the spinal cord, they might be antinociceptive. (Extensively adopted from: <sup>31,57,58</sup>)  
**Abbreviations:** Cannabinoid receptor 1 (CB<sub>1</sub>), Cannabinoid receptor 2 (CB<sub>2</sub>), excitatory motor neuron (EM), interneuron (IN), intrinsic primary afferent neuron (IPAN)

the animal studies. In brief, cannabinoids are usually inhibitory in the GI tract through inhibiting vagal pathway.<sup>10,12,15</sup> Here, we have summarized the major functions of endocannabinoid system in the GI tract:

1. Cannabinoids are anti-nociceptive through both CB<sub>1</sub> and CB<sub>2</sub> receptors. Moreover, enhanced endocannabinoid tone decreases visceral pain in animal models.<sup>16,17</sup>
2. Cannabinoids inhibit gastrointestinal motility through CB<sub>1</sub> receptors in physiologic conditions and CB<sub>1</sub>/CB<sub>2</sub> receptors during inflammation.<sup>18</sup> Cannabinoids inhibit transient lower esophageal sphincter relaxation,<sup>19</sup> delay gastric emptying<sup>20</sup> and inhibit intestinal transit or contractility.<sup>18</sup>

3. Phytocannabinoids and exogenous cannabinoid agonists inhibit the disordered intestinal permeability during inflammation or after exposure to cholera toxin.<sup>21</sup> Moreover, activating CB<sub>1</sub> receptors reduces acid secretion in the stomach.<sup>22</sup>
4. Cannabinoids induce hyperphagia and increase appetite resulting in weight gain. In addition, cannabinoids including both THC and CBD reduce nausea and vomiting through interacting with CB<sub>1</sub>, CB<sub>2</sub> and TRPV<sub>1</sub> receptors as well as through possible interaction with 5-hydroxytryptaminergic (5-HT; serotonergic) system.<sup>12,23</sup>
5. Cannabinoids are anti-inflammatory, and this makes them a potential candidate for the treatment of colitis.<sup>24</sup>
6. Cannabinoids induce apoptosis, are antiproliferative and anti-cancerous.<sup>25</sup>
7. In the liver, the expression of cannabinoid receptors is low. However, the activation of CB<sub>1</sub> receptors is profibrogenic, proinflammatory and pro-steatotic. On the other hand, CB<sub>2</sub> receptors inhibit hepatic fibrogenesis.<sup>26</sup>

Understanding the physiology of endocannabinoid system in the GI tract helps us to define the therapeutic potentials of cannabis and its derivatives in different GI diseases.

### Cannabinoids and Gastrointestinal Disorders

While many pre-clinical studies have proved the benefits of cannabinoids and endocannabinoids in GI diseases, clinical studies targeting endocannabinoid system are restricted. This is basically because of the psychoactive effects of these compounds as well as the legal restrictions.

### Cannabinoids and Nausea/Vomiting

Conventional antiemetics such as 5-HT<sub>3</sub> and NK<sub>1</sub> antagonists are helpful in reducing episodes of vomiting; however, they are not usually helpful in reducing the unpleasant sensation of nausea. In contrast, cannabinoids can inhibit both nausea and vomiting. This has been proved in different clinical trials on chemotherapy induced nausea and vomiting (CINV) by

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using synthetic cannabinoid agonists such as dronabinol, nabilone and levonantradol as well as with THC/CBD mixture (i.e. Sativex). In an earlier study back in 1985, nabilone was compared to prochlorprazine for the treatment of chemotherapy induced emesis. Based on this study, nabilone was superior to prochlorprazine in reducing vomiting episodes.<sup>27</sup> Moreover, a recent study that compared dronabinol and ondansetron for delayed CINV showed these medications are similarly effective and their combination is not superior.<sup>28</sup> Despite these benefits, due to central side effects, cannabinoid based therapy is not considered the first line treatment in patients with CINV.<sup>8,23</sup>

Studies on the effects of smoked cannabis and nausea/vomiting are limited. In a study which compared a group of patients who smoked marijuana before/after chemotherapy and another group who had used THC capsule orally, the former group experienced 70-100% symptom relief, while symptom relief in those who had used THC was 76-88%, suggesting a favorable therapeutic role for smoked cannabis in CINV.<sup>29</sup> In another study, Söderpalm et al. tested the effects of smoked cannabis compared to ondansetron in controlling Ipecac induced nausea and vomiting. Smoked cannabis reduced both nausea and vomiting; however, its effects were modest compared to ondansetron.<sup>30</sup>

A side effect of long-term (generally >5 years) daily marijuana smoking is cannabinoid-induced hyperemesis syndrome, which is particularly observed in male patients and presents with repeated cyclical vomiting and frequent hot bathing. The symptoms usually alleviate after cessation of cannabis smoking. Not all cannabis users develop hyperemesis syndrome. Therefore, the total (cumulative) dose of marijuana, genetic factors, and psychological parameters may contribute to this condition. The pathophysiology of cannabinoid-induced hyperemesis syndrome remains unknown. The few hypotheses which may explain this syndrome are: (a) accumulation of the cannabis derivatives in the brain based on their lipid solubility and long-term half-life, (b) degradation of the cannabis ingredients to some potential emetic metabolites or toxins, (c) delayed gastric emptying induced by cannabis and (d) down-regulation or desensitization of the cannabinoid receptors due to chronic cannabis use.<sup>31,32</sup>

Cyclic vomiting syndrome (CVS) is a functional GI disorder which presents with nausea and vomiting

**Table 1. The Pharmacological Function and the Therapeutic Potential of the Cannabinoid Agonists and Antagonists in the Gastrointestinal Tract**

	<b>Cannabinoid Agonists</b>	<b>Cannabinoid Antagonists</b>
<b>Gastrointestinal motility</b>	Decreased; Rx for diarrhea	Increased; Rx for constipation or gastroparesis
<b>Gastrointestinal secretion</b>	Decreased; Rx of secretory diarrhea	-
<b>Visceral sensation</b>	Decreased; Rx for chest pain of esophageal origin and abdominal pain	-
<b>Nausea and Vomiting</b>	Decreased; Rx for chemotherapy induced nausea and vomiting and cyclic vomiting syndrome	-
<b>Appetite</b>	Increased; cachexia of AIDS	Decreased; Rx for obesity
<b>Inflammation</b>	Decreased; Rx for inflammatory bowel disease	-
<b>Cancer</b>	Anti-cancerous; Rx for colon or pancreatic cancer	-

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and epigastric abdominal pain. CVS presents with stereotypical and recurrent episodes of vomiting and abdominal pain with relatively nausea and vomiting free intervals. The pathophysiology of CVS is unknown.<sup>32</sup> Studies from our group have shown a high rate of cannabis use in a subset of patients with cyclic vomiting syndrome. These patients needed a higher dose of amitriptyline for the control of their CVS attacks compared to non-cannabis users.<sup>33,34</sup> Therefore, it is important to identify cannabinoid induced hyperemesis syndrome as part of the CVS, since a long term goal is decreasing and stopping cannabis use in these patients.

The acute treatment regimen for vomiting attacks in both CVS and cannabinoid-induced hyperemesis syndrome are based on intravenous hydration, intravenous lorazepam due to its sedative effects, anti-emetics and non-narcotic pain medications. Tricyclic antidepressants (TCA) particularly amitriptyline in high doses are recommended for the long-term prophylaxis. Gradual reduction and stopping cannabis use, psychological interventions, anti-anxiety medications and relaxation techniques are necessary in these patients.<sup>32</sup>

Overall, despite their favorable effects in controlling nausea, cannabinoids are not the first line treatment of nausea and vomiting including CINV as their chronic use may also induce hyperemesis syndrome. Their anti-emetic effects are modest compared to other conventional medications. Moreover, their side effects make them unfavorable treatment for nausea and vomiting. On the other hand, medical cannabis including dronabinol which is available in the United States and has antiemetic effects at 5-10 mg per dose three times a day may be effective in a subset of patients with gastroparesis who present with nausea and vomiting. It is important to recognize that prescribing cannabis based medications is very different from chronic daily cannabis smoking, which can lead to the entity termed cannabinoid-induced hyperemesis syndrome. Whether manipulating endocannabinoid levels is effective in controlling nausea and vomiting is the goal of future studies in this field.

### **Cannabinoids and Appetite**

Cannabis stimulates appetite and increases food intake. Therefore, cannabis-derivatives (e.g. dronabinol) or smoking cannabis are potential treatments for patients with AIDS-associated loss of appetite and cachexia.<sup>6,8</sup>

On the other hand, to our knowledge, no trial has tested the effects of smoked cannabis in inducing appetite or increasing weight among patients with cancer. Moreover, the data on oral THC as the stimulator of appetite in patients with cancer are not conclusive. Interestingly, recent studies have questioned the general belief of higher rate of obesity in cannabis smokers. Based on two large cohorts including 43,093 and 9282 respondents among US adults aged 18 years or older (2001-2003), the adjusted prevalence of obesity was about 8% lower in participants reporting the use of cannabis at least 3 days per week.<sup>35</sup> Therefore, although cannabis may stimulate appetite, its effect on weight gain is not well confirmed. Delayed gastric emptying<sup>20</sup> or potential tolerance to chronic cannabis use<sup>36</sup> may explain lower weight in chronic cannabis users.

### **Cannabinoids and IBS**

IBS is a functional GI disorder presenting with abdominal pain/discomfort and disturbed bowel habits. The pathophysiology of IBS is not well understood and its treatment is underdeveloped. In IBS endocannabinoid signaling is altered compared to normal population.<sup>37</sup> Moreover, cannabinoids can affect both GI motility and visceral sensation.<sup>12</sup> Therefore, they are potential candidates for the treatment of IBS especially when it presents with diarrhea.

Studies on the effect of smoked cannabis in IBS are lacking. Based on a clinical trial, dronabinol (5mg) increased colonic compliance and decreased colonic contraction in IBS patients with diarrhea or alternating bowel habits. These responses were varied based on polymorphisms of FAAH and CB<sub>1</sub> encoding genes. In this study, dronabinol did not change sensation scores for pain and gas.<sup>38</sup> In another study from the same group, treatment with dronabinol did not alter gut transit in IBS-D, but tended to decrease colonic transit in subjects with a specific polymorphism at CB<sub>1</sub> encoding gene.<sup>39</sup> Another study, which tested the effects of dronabinol (up to 10mg) on visceral perception to rectal distension in IBS vs. health controls, showed dronabinol does not affect baseline and stimulated rectal perception.<sup>40</sup>

Overall the effects of THC as an effective component of cannabis on GI motility in IBS are variable and its effect on abdominal pain and visceral sensation is not promising. Whether manipulating endocannabinoid system is effective in IBS needs further investigations.

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#### Cannabinoids and IBD

Although there is not a well designed case-control study, smoking cannabis looks to be common among patients with inflammatory bowel disease (IBD). Based on the available studies, 39-49% of patients were past/lifetime and 12-14% of them were current marijuana users,<sup>41,42</sup> and 18-32% of IBD patients have used marijuana for their IBD symptoms.<sup>41,43</sup> Smoking cannabis was more common among patients with Crohn's disease and a better response to cannabis was observed in these patients.<sup>42</sup> On the other hand, long-term cannabis use was correlated with the risk of surgery in patients with Crohn's disease,<sup>43</sup> questioning the therapeutic benefits of cannabis in IBD. Recently, a clinical trial on a small number of patients with Crohn's disease showed that 8 weeks of smoking cannabis (standardized to 115mg of THC; twice daily) decreased Crohn's disease activity index (CDAI) more significantly compared to placebo; however, after 2 weeks wash-out period, CDAI was not different in both groups suggesting a temporary but not sustained benefit for smoking cannabis in these patients. C-reactive protein levels did not change after smoking cannabis and endoscopic findings were not collected.<sup>44</sup> Although these findings are somehow promising, the temporary effect of cannabis as well as the increased risk of surgery in patients with Crohn's disease who were long-term users of cannabis questions whether medical cannabis is effective in IBD as advertised in the media and among patients and physicians.

At the moment, we should be cautious in prescribing cannabis for patients with IBD. Larger studies with cannabis or synthetic cannabinoids as well as the modulators of endocannabinoid levels (e.g. FAAH inhibitors) are recommended.

#### Cannabinoids as Anti-Nociceptive Agents

As mentioned above, the effect of THC on abdominal pain and visceral sensation in IBS patients is not promising. However, interestingly a recent double-blind controlled trial showed that dronabinol (5mg b.i.d. for 4 weeks) was superior to placebo in increasing pain threshold and decreasing the frequency and intensity of non-reflux related non-cardiac chest pain. No significant adverse effects were noted in this study.<sup>45</sup>

Therefore, the origin of pain may define the therapeutic efficacy of cannabinoid based medicine in GI diseases with pain. More studies with different

regimen are necessary to evaluate the effects of cannabis and its derivatives on visceral sensation and pain.

#### Cannabinoids and Hepatitis C

Using cannabis as a street drug is common among people with or without hepatitis C. There is a general belief among patients with hepatitis C that cannabis helps with the adverse effects of their medications. This has been shown in studies indicating less adverse effects of interferon and the adherence to HCV treatment in cannabis users or those who were receiving oral cannabinoid-containing medications.<sup>46,47</sup> On the other hand, a recent study has shown no association between cannabis use and the likelihood of completing a full course of HCV therapy, interruption of therapy or sustained virological response.<sup>48</sup> As the newer and much more effective HCV therapeutic regimens which lack interferon are introduced, the side effects of interferon therapy (e.g. nausea, cachexia, depression) are disappearing and therefore, there will not be a significant indication for the medical cannabis in HCV just based on its potentials in alleviating therapeutic side effects in early future.

Studies on the effects of cannabis and its effect on the progression of liver damage are not conclusive. While some studies have shown that daily cannabis use is associated with liver fibrosis and steatosis in patients with hepatitis C,<sup>49-50</sup> others have shown no association between the progression of liver damage and smoking cannabis.<sup>48-52</sup>

#### Adverse Effects of Cannabis Use

The disorders related to cannabis are majorly classified as: (1) cannabis intoxication, (2) cannabis use disorder, and (3) cannabis withdrawal.<sup>53-55</sup> When recreational cannabis is allowed and medical cannabis is legalized in different states, practicing physicians may see more patients presenting with adverse effects of cannabis use. Many of the adverse effects are self-limited and mild, although psychological interventions, replacement therapies and symptomatic treatment might be necessary.

Cannabis intoxication presents with physiologic and psychiatric presentations of smoking cannabis. Briefly, patients present with anxiety, panic and psychotic symptoms, red eye, tachycardia, dry mouth and increased appetite.<sup>53,54</sup>

Cannabis use disorder includes daily or near daily heavy or regular cannabis use for a long duration which may present with cannabis dependence syndrome

(which is majorly psychological) in around 1 in 10 users, tolerance as what possibly occurs in cannabis hyperemesis syndrome and disturbed personal and social function. Chronic cannabis smoking may cause chronic bronchitis, psychotic symptoms especially in those with other risk factors of these disorders, cognitive impairment in long-term users and after abstinence and impaired educational attainment among adolescents.<sup>53,54</sup>

Cannabis withdrawal presents with psychiatric symptoms such as insomnia, anxiety, depression, appetite disturbance and physical symptoms of impaired cannabis signaling such as abdominal pain, headache, tremor, and restlessness. Most symptoms usually occur on the first day after abstinence, peak on day 2-6 and are abolished within 14 days.<sup>55</sup>

Another big concern regarding cannabis abuse is related to synthetic cannabinoids. These drugs, which are predominantly full and potent agonists of CB<sub>1</sub> receptors, may induce dangerous side effects such as seizure, hallucination, tachycardia and arrhythmia. They may also affect non-cannabinoid pathways and produce severe intoxication.<sup>9</sup> Therefore, we should also be aware of the clinical manifestations of synthetic cannabinoid abuse.

### Cannabinoid Receptors Antagonists

Reducing the endocannabinoid tone enhances GI motility and decreases the appetite. Therefore, while the purpose of medical cannabis is the induction of endocannabinoid response, reducing endocannabinoid tone with the cannabinoid receptors antagonists is a potential treatment for constipation and obesity. The most famous compound in this area is the CB<sub>1</sub> inverse agonist Rimonabant, which was approved in Europe as an anti-obesity medication. This drug was withdrawn from the market based on its serious side effects such as depression and increased suicidal tendency.<sup>56</sup>

With the invention of peripherally restricted cannabinoid receptors antagonists, we may see other substitutes for Rimonabant with clinical potentials in the future.

### RECOMMENDATIONS AND CONCLUSIONS

The pharmacological function of cannabinoid agonists and antagonists may define the potential therapeutic indication of these compounds. These have been summarized in Table 1.

Medical cannabis is effective in patients with chemotherapy induced nausea and vomiting and in

cachexia associated with AIDS; however, the evidence to support the role of medical cannabis in other GI diseases is poor. In some cases, cannabis use may associate with the progression of the disease (e.g. hepatitis C) or poor outcome (e.g. risk of surgery in Crohn's disease). Despite the misguided advertisements for cannabis as a therapy for different GI diseases, we should be cautious in prescribing medical cannabis and should communicate with our patients regarding the adverse effects as well as the limitations of current studies in the field. This may change by larger and well-controlled studies in future.

For patients with CVS who are active cannabis users and patients with cannabinoid-induced hyperemesis syndrome, we recommend gradual decrease and stopping cannabis. During vomiting episodes, lorazepam plus anti-emetics are helpful and for the prophylaxis of vomiting attacks, high-doses of TCAs are recommended.

We believe the compounds that selectively target endocannabinoid metabolism and degradation are the potential medications of future for human diseases including GI disorders. ■

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