DEPARTMENT OF HEALTH

Irritable Bowel Syndrome (IBS) Issue Brief

INCLUDING IBS AND IBS-D

OCTOBER 2022

Introduction

This briefing was prepared in response to petitions to consider adding irritable bowel syndrome (IBS) and irritable bowel syndrome with diarrhea (IBS-D) as new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, members of the Medical Cannabis Review Panel, and interested members of the public, scientific studies of cannabis products as a therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) were included, especially if there are few clinical trials or observational studies. Interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses; however, surveys published in peer-reviewed journals were included for completeness. Published recommendations or opinions of national medical organizations were also included.

Searches for published clinical trials and observational studies of cannabis therapy were conducted using the National Library of Medicine's Medline using key word searches appropriate for the petitioned condition. Articles identified as clinical trials, observational studies, or review articles were collected and reviewed. References in the identified articles were examined to ensure all the articles associated with the petitioned condition were identified and included. Moreover, clinicaltrials.gov, a federal government-maintained website responsible for tracking current clinical trials funded, was used identify any ongoing or completed clinical trials.

Definition

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by abdominal pain or discomfort, and irregular bowel movements that can result in diarrhea, constipation, both diarrhea and constipation, or bloating. These symptoms can occur without any visible signs of damage or disease within the digestive tract. Symptom severity can range from debilitating to mild or moderate. Further, IBS is often associated with additional somatic comorbidities (conditions that affect the body), psychiatric conditions, and visceral sensitivity (Enck et al., 2016).

IBS is thought to be caused by a functional gastrointestinal disorder, resulting in disrupted interactions between the brain and the gut. The associated problem between the brain and the gut leads to increased sensitivity and changes in bowel muscle contractions. More sensitive bowels experience more bloating and pain, whereas irregular bowel muscle contractions result in diarrhea, constipation, or both (Ford et al., 2020).

A commonly used diagnostic tool for IBS (Rome IV criteria) categorizes IBS into three main subtypes, IBS-C, IBS-D, and IBS-M. IBS-C (constipation) occurs when more than a quarter of a patient's stools are hard and lumpy, while less than a quarter of their stools are loose or watery. IBS-D (diarrhea) occurs when more than a quarter of a patient's stools are loose or watery, while less than a quarter of stools are hard or lumpy. Lastly, IBS-M (mixed) occurs when more than a quarter of a patient's stools is loose, or watery and more than a quarter of a patient's stools are hard and lumpy (Chey et al., 2015).

Another common gastrointestinal (GI) disorder already approved as a condition for medical cannabis is irritable bowel disease (IBD). Unlike IBS, which is characterized by a gut-brain disorder, IBD, which encompasses Crohn's disease (CD) and Ulcerative colitis (UC), is characterized by chronic relapsing inflammation and immune activity (Abdul Rani et al., 2016). However, IBS and IBD have similarities. For example, both IBD and IBS patients are predisposed to psychological comorbidities, specifically depression and anxiety (Abdul Rani et al., 2016). Further, studies have found that depression can increase a patient's probability for developing increased inflammation (Fagundes et al., 2013, Johnson et al., 2002). Further, recent studies in the U.S., Sweden, and the U.K. noted that like IBD, IBS patients experience a genetic mutation in their immune activation markers, suggesting a similar pathway to disease development (Abdul Rani et al., 2013). However, the level of inflammation seen in IBD patients is markedly greater than that seen in IBS patients and inflammation seen in IBD patients is often ongoing and slow to resolve, while IBS inflammation is variable, or even absent (Abdul et al., 2016). Finally, both IBD and IBS patients experience abnormal gut microbiota (Abdul et al., 2016). However, unlike IBS, IBD is an organic disease evidenced by inflammation in the mucosal section of the stomach, whereas IBS is seen as a spectrum of functional disorder, with no evidence of organic disease (Abdul et al., 2016). Overall, evidence supports an intimate interlink between IBS and IBD, but with different presentations and outlooks. Ultimately, more large-scale research is needed to define a clear connection.

Epidemiology

IBS results in significant reductions in health-related quality of life and work productivity. Approximately 12% of people living in the United States have IBS. Women are two times more likely to develop IBS than men, and people younger than 50 years of age are at an increased risk of developing IBS compared to those over 50 years (Chey et al., 2015). Further, IBS is estimated to account for $3.1 million ambulatory care visits and 5.9 million prescriptions annually, with the total indirect and direct costs exceeding $20 billion (Chey et al., 2015). Over time, an estimated 2% to 18% of clinical-based IBS patients experience worsening symptoms; 30% to 50% patients remain unchanged; and 12% to 38% experience improved symptoms (Chey et al., 2015).

Factors that increase a person's likelihood of developing IBS include a family history of IBS, a history of stress, difficult/traumatic life events or abuse, severe digestive tract infection, small intestinal bacterial overgrowth, and food intolerance/sensitivity (Chey et al., 2015).

Diagnosis

IBS diagnosis is based on the presence of characteristic symptoms and exclusion of select diseases, including other gastroenterological disease such as colon cancer, celiac disease, or inflammatory bowel disease. The distinguishing features of IBS in accordance with current diagnostic standards, and Rome III criteria, include abdominal pain discomfort or altered bowel habits. Stool consistency is used to distinguish between the three subtypes of IBS, because it has been identified as a more consistent marker of disease compared to stool frequency as a marker. Stool consistency can be assessed using the Bristol Stool Form Scale (Chey et al., 2015).

Diagnostic Criteria for Irritable Bowel Syndrome (IBS) With Subtypes includes:

Recurrent abdominal pain or discomfort at least three days a month associated with two or more of the following: reduced abdominal pain with defecation, onset associated with a change in frequency of stool, or onset associated with a change in form (appearance) of stool (Chey et al., 2015).

IBS with constipation (IBS-C) is defined as hard or lumpy stools ≥25% and loose or watery stools <25% of bowel movements. IBS with diarrhea (IBS-D) is defined as loose or watery stools ≥25% and hard or lumpy stools <25% of bowel movements. Mixed IBS (IBS-M) is defined as hard or lumpy stools ≥25% and loose or watery stools ≥25% of bowel movements (Chey et al., 2015).

While diagnosis of IBS-D or IBS-C is relatively straightforward, the diagnosis of patients with IBS-M presents a unique challenge. Therefore, a detailed history of a patients mixed bowel patterns is required to better understand the underlying disease state (Chey et al., 2015). Further, the consideration of all prescription and over-the-counter medications is needed to determine how they might affect IBS symptoms (Chey et al., 2015).

In addition to the identification of symptom-based criteria, a detailed assessment to eliminate the potential for alternative disease is required to finalize the diagnosis. A patient with clear IBS symptoms combined with an absence of diagnostic markers indicative of other gastrointestinal related disorders, can be diagnosed as having IBS with some level of accuracy (Chey et al., 2015).

Current Therapies

Treatment of IBS focuses on relieving symptoms so a patient can live a normal life. Mild signs and symptoms can often be controlled by reducing stress and by making changes in diet and lifestyle. Lifestyle changes include avoiding foods that trigger symptoms, eating high-fiber foods, drinking plenty of fluids, exercising regularly, and getting enough sleep. Patients may also need to eliminate high-gas foods, gluten, and consume a low-FODMAPS diet (a diet low in fermentable carbohydrates) (Chey et al., 2015). A meta-analysis of the low-FODMAP diet found

that the diet was effective at improving patient well-being and reducing symptoms (van Lanen et al., 2021). However, the impact the low-FODMAP diet might have on the gut microbiome community is still unknown, and more research needs to be conducted to determine the long-term effects of the low-FODMAP (van Lanen et al., 2021). Further, many studies included in the meta-analysis had large variation in control diets between studies, and the content of these controls have not been well established (van Lanen et al., 2021).

Medications

A doctor may recommend medication to relive IBS symptoms dependent on the type of IBS a patient is suffering from.

Antidiarrheal medication, such as loperamide, is often used as primary treatment for IBS-D. It can be used to inhibit peristalsis (involuntary, wave-like muscle contractions that push content forward), which prolongs gut transit and reduces fecal volume (Chey et al., 2015). However, two randomized controlled trials focusing on IBS-D and IBS-M patients found no benefit of loperamide compared to the placebo group for the overall reduction of IBS symptoms (Chey et al., 2015). Loperamide was able to reduce stool frequency, increase stool consistency and could be used as a diarrheal prophylactic (Chey et al., 2015).

Serotonin agents such as Alosetron, a 5-HT_3 antagonist has been approved for use in the United States for the treatment of women with severe, debilitating IBS-D when the patient has not responded well to traditional medical therapies (Chey et al., 2015). Alosetron has been found to improve IBS-D symptoms in women and men for up to a year, with patients receiving a 15% reduction in symptoms compared to the placebo.

Notably, the American College of Gastroenterology Functional Bowel Disorders Task Forces concluded that certain antispasmodics (otilonium, hyoscine, cimetropium, pinaverum, and dicyclomine) can provide short-term symptomatic relief to IBS patients. However, because some patients have an exaggerated gastrocolonic reflex, antispasmodics may function better as a treatment for upper abdominal pain after eating or loose stools (Chey et al., 2015). Dose-dependent adverse events, such as constipation, fatigue, dry mouth, dizziness, and blurred vision have been known to occur. Peppermint oil has been identified as a potential antispasmodic treatment in several small clinical trials. However, some patients may experience severe reflux symptoms (Chey et al., 2015). Laxatives, such as polyethylene glycol, are frequently recommended as a therapy for IBS-C, and clinical trials have demonstrated an improvement in stool frequency and consistency. However, it has not been shown to improve abdominal pain or bloating (Chey et al., 2015). Stimulant laxatives have also been used as a therapy for IBS-C patients, but there have been few randomized controlled trials evaluating its efficacy (Chey et al., 2015).

Certain agents, such as lubiprostone, can stimulate intestinal fluid secretion and improve global bowel, and abdominal symptoms in IBS-C patients (Chey et al., 2015). Two phase-three clinical trials found a significantly higher percentage in patients treated with lubiprostone compared to placebo controls (Chey et al., 2015).

Alternatively, a different agent, Linaclotide, has been identified as a treatment for IBS-C patients. Specifically, a 2013 meta-analysis found that Linaclotide reduced IBS-C severity

compared to placebo controls (Chey et al., 2015). Linaclotide was also found to be somewhat effective at reducing the likelihood of diarrhea (Lacy et al., 2009). As a result, Linaclotide treatment is most effective at improving stool frequency a week after treatment initiation, whereas abdominal pain and bloating may take 8 to 12 weeks before maximize effects are felt (Chey et al., 2015).

The use of probiotics and antibiotics has been explored as a treatment for IBS (Chey et al., 2015). Specifically, a meta-analysis of 35 randomized control trials found that probiotics improved overall IBS symptoms including abdominal pain, bloating, and flatulence (Ford et al., 2014). However, there was some variability in the probiotics used and grouping methods employed that limited comparability (Ford et al., 2014). As a result, higher-quality studies are needed, as the current literature does not allow for any recommendation regarding the use of specific probiotic preparations for IBS (Chey et al., 2015). Alternatively, antibiotics such as rifaximin, have been shown to demonstrate therapeutic gains of 9% to 10% for global symptoms in no constipated IBS patients (Menee et al., 2012). However, clinical studies suggest that many rifaximin responders will eventually develop recurrent IBS symptoms (Chey et al., 2015). Overall, the role of antibiotics such as rifaximin remains unknown, and antimicrobial resistance due to overuse remains a significant concern (Chey et al., 2015).

Recently, antidepressants have become a widespread treatment option for patients with moderate to severe IBS. A meta-analysis of 17 randomized controlled trials found that antidepressants were effective at reducing abdominal pain (Dekel et al., 2013). However, Tricyclic antidepressants were shown to cause dose-dependent constipation, whereas selective serotonin-reuptake inhibitors can cause diarrhea. Further, although selective norepinephrine-reuptake inhibitors offer benefits for anxiety, depression, and somatic pain, they have yet to be evaluated as an efficacious treatment for IBS (Chey et al., 2015). Psychological therapies have been identified as an alternative or adjunctive therapy for IBS patients. Specifically, a meta-analysis of 32 studies found that 10 different psychological therapies were effective at reducing IBS symptoms (Ford et al., 2014). However, despite these results, access to behavioral therapy remains limited.

Alternative medicines, such as acupuncture, have been considered as a therapy for treatment of IBS (Hussain et al., 2006). However, a meta-analysis of five studies found that acupuncture was no better at reducing IBS symptoms compared to those not receiving acupuncture (Manheimer et al., 2012). Studies evaluating herbal remedies have yielded mixed results. There is a lack of an understanding of active ingredients involved. And there is no clear standardized treatment. Overall, current therapies for IBS are available, but rely on patient-physician relationships, and holistic approaches that utilize lifestyle changes, dietary interventions, medication, and behavioral strategies to maximize treatment of IBS (Chey et al., 2015).

Pre-clinical Research

Animal and human studies have shown that cannabinoids play an important role in the regulation of gastric and intestinal secretion. Said cannabinoids reduce production of gastric acid secretion by activating the CB1 receptors. Recent studies have also identified a potential pathophysiologic mechanism for IBS; specifically, deficiencies in the endocannabinoid system (Hill et al., 2017, Brugnatelli et al., 2020). Pre-clinical studies have shown a direct connection

between the endocannabinoid system and regulation of gastrointestinal motility (Storr et al., 2008). In fact, activation of the cannabinoid 1 (CB1) and the cannabinoid 2 (CB2) receptors reduce motility, limit secretion, and decrease hypersensitivity in the gut. Further, in mice models of post-inflammatory IBS, inhibition of transit by endocannabinoid-like compounds has been shown to block CB1 receptor antagonists, therefore modulating gut motility (Hasenoehrl et al., 2016). Additionally, research by Vianna et al., 2012 reported that a deletion of the CB1 receptors in the vagal nerves of mice caused increased gastrointestinal motility. Despite the promising pathophysiologic mechanism, studies examining the impact of an endocannabinoid deficiency on IBS are limited.

Clinical Trials

A clinical trial by Wong et al. in 2011 evaluated the effect of dronabinol on colonic motility and sensation in patients with IBS (Wong et al., 2011). In this study the authors compared IBS patients who received dronabinol (sometimes referred to as marinol), a synthetic tetrahydrocannabinol (THC), to IBS patients who did not receive dronabinol. The authors examine colonic motility (the degree to which the bowel moves waste through it), and colonic compliance (a measure of the pressure needed to reach half the maximum volume of the colon). Notably, the authors found patients who received dronabinol experienced reduced colonic motility and improved colonic compliance compared to a placebo control. The effects were most pronounced in those with IBS-D and IBS with alternating symptoms. These findings presented a promising new treatment for IBS and specifically, IBS-D. In 2012, Wong et al. attempted to recreate the dronabinol effects in IBS-D patients specifically. However, the randomized controlled trial conducted by Wong et al. in 2012 failed to reproduce the findings seen in 2011 (Wong et al. 2012). In addition, a study by Klooker at al., 2011, showed that the cannabinoid receptor agonist delta-9-tetrahydrocannabinols (THC) had no effect on rectal distension or rectal sensitivity in healthy volunteers and IBS patients. Moreover, a placebo-controlled crossover study (a study where patients receive both the treatment and the placebo at different times during a study) reported no significant difference in IBS patient pain scores between CBD and placebo treatments. However, this study was small scale and only recruited women for the study (Anne-Claire B. et al., 2021). Finally, a small clinical trial investigating the impact of cannabidiol therapy on IBS patients found at the group level there was no difference in the pain score of those who received the cannabidiol therapy compared to those who did not receive the cannabidiol therapy (van Orten-Luiten et al., 2021). Overall, while some studies, such as the 2011, Wong et al. have shown the promising potential for dronabinol, several more recent studies have failed to reproduce these findings. Thus, more large-scale clinical trials are needed.

Ongoing Clinical Trials

A search for current ongoing clinical trials was conducted on clinicaltrials.gov. Search terms specific to cannabis and IBS were used to identify clinical trials. Search terms for IBS included Irritable Bowel Syndrome, IBS, IBS-D, IBS-C, and IBS-M. Search terms for Cannabis included cannabis, THC, marijuana, and dronabinol. Currently there are no ongoing clinical trials investigating the potential role of cannabis as a treatment for IBS.

Observational Studies

A retrospective nationwide cohort study of 7,163 patients with IBS sought to examine the potential association between cannabis use and IBS (Choi et al., 2022). The authors examined hospital readmission rates between IBS patients who reported using cannabis and IBS patients who did not use cannabis (Choi et al., 2022). When the authors adjusted for additional variables, they found no significant difference in hospital readmission rates between the IBS cannabis users and the IBS cannabis non-users (Choi et al., 2022). However, Choi et al. did note that IBS patients who used cannabis had lower in-hospital resource utilization during IBS-specific readmission (Choi et al. 2022). Therefore, the authors found that cannabis use had no impact on IBS-specific 30-day hospital readmission rates but did reduce total hospitalization cost and charges.

Adejumo et al. conducted a national survey, using the international classification of disease, 9th edition codes to identify individuals with Cannabis Use Disorder (CUD) and IBS. They found that patients with CUD were significantly more likely to have IBS compared to patients without CUD (Adejumo et al. 2019). These finding suggest that the abnormal use of cannabis may either contribute to the development or exacerbation of IBS and its symptoms. Adding to this, a study of 31,272 patients by Patel et al., 2020, found that patients with CUD had a higher odd for IBS hospitalization compared to patients without Cannabis Use Disorder (Patel et al. 2020). This suggests the use of cannabis among those with CUD may be associated with the development of IBS or exacerbation of IBS symptoms. Therefore, while there is a potential benefit associated with the use of cannabis, the improper use of cannabis poses some risk to the development and aggravation of IBS.

In 2020, a retrospective cohort study of 9,393 IBS patients (246 cannabis users and 9,147 nonusers), reported that cannabis use may decrease inpatient health-care utilization in IBS patients. Specifically, cannabis users were less likely to have upper gastrointestinal endoscopy and lower gastrointestinal endoscopy performed compared to non-cannabis users (Desai et al., 2020). Cannabis users experienced significantly shorter hospital length stays compared to non-cannabis users (Desai et al., 2020, Choi et al., 2022). In contrast, a study by Adeyinka et al., 2019, reported a higher likelihood of hospitalization among people who use cannabis conflicting with prior reports of a shortened stay. This paper also noted that an elevated state of anxiety might countermand the effects of cannabis on the endocannabinoid system (Adeyika et al., 2019). In conclusion, while cannabis as a therapy for IBS shows promise, the data remains inconclusive and more large-scale clinical trial research is needed.

In contrast to IBS, IBD research suggests that the use of small doses of cannabis can help reduce inflammation and reduces the overall IBD symptomology (McCallum et al., 2014, Perisetti et al., 2020). However, consumption of cannabis at high levels can exacerbate IBD symptoms and increase a patient's likelihood to be hospitalized due to severe IBD (UC and CD) (McCallum et al., 2014, Perisetti et al., 2020). Therefore, extreme cause should be taken when using cannabis as a therapy for IBD.

National Medical Organization Recommendations

In 2013, the National Institute of Diabetes and Digestive and Kidney Disease funded a study to examine the relationship between cannabinoids and fasting colonic motility. The study found that cannabinoid agonists reduced fasting colonic motility in patients with non-constipated irritable bowel syndrome. However, to date the American College of Gastroenterology and the National Institute of Diabetes and Digestive and Kidney Disease have made no recommendation regarding the use of medical cannabis as a treatment for IBS.

References

Abdul Rani, R., Raja Ali, R. A., & Lee, Y. Y. (2016). Irritable bowel syndrome and inflammatory bowel disease overlap syndrome: pieces of the puzzle are falling into place. *Intestinal research*, *14*(4), 297–304. https://doi.org/10.5217/ir.2016.14.4.297

Adejumo, A. C., Ajayi, T. O., Adegbala, O. M., & Bukong, T. N. (2019). Higher odds of irritable bowel syndrome among hospitalized patients using cannabis: a propensity-matched analysis. *European journal of gastroenterology & hepatology*, *31*(7), 756–765. https://doi.org/10.1097/MEG.0000000000001382

Brugnatelli, V., Turco, F., Freo, U., & Zanette, G. (2020). Irritable Bowel Syndrome: Manipulating the Endocannabinoid System as First-Line Treatment. *Frontiers in neuroscience*, *14*, 371. https://doi.org/10.3389/fnins.2020.00371

Chey, W. D., Kurlander, J., & Eswaran, S. (2015). Irritable bowel syndrome: a clinical review. JAMA, 313(9), 949–958. https://doi.org/10.1001/jama.2015.0954

Choi, C., Abougergi, M., Peluso, H., Weiss, S. H., Nasir, U., & Pyrsopoulos, N. (2022). Cannabis Use is Associated with Reduced 30-Day All-cause Readmission Among Hospitalized Patients with Irritable Bowel Syndrome: A Nationwide Analysis. *Journal of clinical gastroenterology*, *56*(3), 257–265. https://doi.org/10.1097/MCG.0000000000001498

Desai, P., Mbachi, C., Vohra, I., Salazar, M., Mathew, M., Randhawa, T., Haque, Z., Wang, Y., Attar, B., & Paintsil, I. (2020). Association Between Cannabis Use and Healthcare Utilization in Patients with Irritable Bowel Syndrome: A Retrospective Cohort Study. *Cureus*, *12*(5), e8008. https://doi.org/10.7759/cureus.8008

Drossman, D. A., Chey, W. D., Johanson, J. F., Fass, R., Scott, C., Panas, R., & Ueno, R. (2009). Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome--results of two randomized, placebo-controlled studies. *Alimentary pharmacology & therapeutics*, *29*(3), 329–341. https://doi.org/10.1111/j.1365-2036.2008.03881.x

Enck, P., Aziz, Q., Barbara, G., Farmer, A. D., Fukudo, S., Mayer, E. A., Niesler, B., Quigley, E. M., Rajilić-Stojanović, M., Schemann, M., Schwille-Kiuntke, J., Simren, M., Zipfel, S., & Spiller, R. C. (2016). Irritable bowel syndrome. *Nature reviews. Disease primers*, *2*, 16014. https://doi.org/10.1038/nrdp.2016.14

Fagundes, C. P., Glaser, R., Hwang, B. S., Malarkey, W. B., & Kiecolt-Glaser, J. K. (2013). Depressive symptoms enhance stress-induced inflammatory responses. *Brain, behavior, and immunity*, *31*, 172–176. https://doi.org/10.1016/j.bbi.2012.05.006

Ford, A. C., Moayyedi, P., Lacy, B. E., Lembo, A. J., Saito, Y. A., Schiller, L. R., Soffer, E.

E., Spiegel, B. M., Quigley, E. M., & Task Force on the Management of Functional Bowel Disorders (2014). American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. *The American journal of gastroenterology*, *109 Suppl 1*, S2–S27. https://doi.org/10.1038/ajg.2014.187

Ford, A. C., Quigley, E. M., Lacy, B. E., Lembo, A. J., Saito, Y. A., Schiller, L. R., Soffer, E. E., Spiegel, B. M., & Moayyedi, P. (2014). Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: systematic review and meta-analysis. *The American journal of gastroenterology*, *109*(9), 1350–1366. https://doi.org/10.1038/ajg.2014.148

Ford, A. C., Sperber, A. D., Corsetti, M., & Camilleri, M. (2020). Irritable bowel syndrome. *Lancet (London, England)*, *396*(10263), 1675–1688. https://doi.org/10.1016/S0140-6736(20)31548-8

Hasenoehrl, C., Taschler, U., Storr, M., & Schicho, R. (2016). The gastrointestinal tract – a central organ of cannabinoid signaling in health and disease. *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society*, *28*(12), 1765–1780. https://doi.org/10.1111/nmo.12931

Hill, K. P., & Palastro, M. D. (2017). Medical cannabis for the treatment of chronic pain and other disorders: misconceptions and facts. *Polish archives of internal medicine*, *127*(11), 785–789. https://doi.org/10.20452/pamw.4123

Johnson, J. D., O'Connor, K. A., Deak, T., Stark, M., Watkins, L. R., & Maier, S. F. (2002). Prior stressor exposure sensitizes LPS-induced cytokine production. *Brain, behavior, and immunity*, *16*(4), 461–476. https://doi.org/10.1006/brbi.2001.0638

Klooker, T. K., Leliefeld, K. E., Van Den Wijngaard, R. M., & Boeckxstaens, G. E. (2011). The cannabinoid receptor agonist delta-9-tetrahydrocannabinol does not affect visceral sensitivity to rectal distension in healthy volunteers and IBS patients. *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society*, *23*(1), 30–e2. https://doi.org/10.1111/j.1365-2982.2010.01587.x

Lacy, B. E., & Chey, W. D. (2009). Lubiprostone: chronic constipation and irritable bowel syndrome with constipation. *Expert opinion on pharmacotherapy*, *10*(1), 143–152. https://doi.org/10.1517/14656560802631319

McCallum, R. W., & Bashahati, M. (2014). Cannabis in gastrointestinal disorders. *Practical Gastroenterology*, *38*(12), 36-46.

Manheimer, E., Wieland, L. S., Cheng, K., Li, S. M., Shen, X., Berman, B. M., & Lao, L. (2012). Acupuncture for irritable bowel syndrome: systematic review and meta-analysis. *The American journal of gastroenterology*, *107*(6), 835–848. https://doi.org/10.1038/ajg.2012.66

Menees, S. B., Maneerattannaporn, M., Kim, H. M., & Chey, W. D. (2012). The efficacy and safety of rifaximin for the irritable bowel syndrome: a systematic review and meta-analysis. *The American journal of gastroenterology*, *107*(1), 28–36. https://doi.org/10.1038/ajg.2011.355

Patel, R. S., Goyal, H., Satodiya, R., & Tankersley, W. E. (2020). Relationship of Cannabis Use Disorder and Irritable Bowel Syndrome (IBS): An Analysis of 6.8 Million Hospitalizations in the United States. *Substance use & misuse*, *55*(2), 281–290. https://doi.org/10.1080/10826084.2019.1664591

Perisetti, A., Rimu, A. H., Khan, S. A., Bansal, P., & Goyal, H. (2020). Role of cannabis in inflammatory bowel diseases. *Annals of gastroenterology*, *33*(2), 134–144. https://doi.org/10.20524/aog.2020.0452

Storr, M. A., Yüce, B., Andrews, C. N., & Sharkey, K. A. (2008). The role of the endocannabinoid system in the pathophysiology and treatment of irritable bowel syndrome. *Neurogastroenterology and motility: the official journal of the European Gastrointestinal Motility Society*, *20*(8), 857–868. https://doi.org/10.1111/j.1365-2982.2008.01175.x

van Lanen, A. S., de Bree, A., & Greyling, A. (2021). Efficacy of a low-FODMAP diet in adult irritable bowel syndrome: a systematic review and meta-analysis. *European journal of nutrition*, *60*(6), 3505–3522. https://doi.org/10.1007/s00394-020-02473-0

van Orten-Luiten, A. B., de Roos, N. M., Majait, S., Witteman, B., & Witkamp, R. F. (2022). Effects of Cannabidiol Chewing Gum on Perceived Pain and Well-Being of Irritable Bowel Syndrome Patients: A Placebo-Controlled Crossover Exploratory Intervention Study with Symptom-Driven Dosing. *Cannabis and cannabinoid research*, *7*(4), 436–444. https://doi.org/10.1089/can.2020.0087

Wong, B. S., Camilleri, M., Busciglio, I., Carlson, P., Szarka, L. A., Burton, D., & Zinsmeister, A. R. (2011). Pharmacogenetic trial of a cannabinoid agonist shows reduced fasting colonic motility in patients with nonconstipated irritable bowel syndrome. *Gastroenterology*, *141*(5), 1638–47.e477. https://doi.org/10.1053/j.gastro.2011.07.036

Wong, B. S., Camilleri, M., Eckert, D., Carlson, P., Ryks, M., Burton, D., & Zinsmeister, A. R. (2012). Randomized pharmacodynamic and pharmacogenetic trial of dronabinol effects on colon transit in irritable bowel syndrome-diarrhea. *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society*, *24*(4), 358–e169. https://doi.org/10.1111/j.1365-2982.2011.01874.x

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