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Exploration of irritable bowel syndrome pathogenesis and treatment approaches

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Thesis

EXPLORATION OF IRRITABLE BOWEL SYNDROME PATHOGENESIS AND TREATMENT APPROACHES

by

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ABSTRACT

Irritable Bowel Syndrome (IBS) manifests in patients through diverse symptoms, including abdominal pain, altered stool frequency, inconsistent stool consistency, and bloating. Investigating the root cause of IBS and exploring effective treatment options are crucial for advancing therapeutic approaches and providing relief to affected individuals. The current speculative pathophysiology of IBS encompasses five prominent theories: post-infection immune response, serotonin dysregulation, bacterial overgrowth, brain-gut interaction, and genetic factors. Many IBS patients opt for nonpharmacological treatments, with a focus on well-studied interventions such as exercise, diet modification, FODMAP consumption, fiber intake, and probiotic supplementation. Additionally, emerging research suggests potential benefits from alternative approaches like hypnotherapy, cognitive behavioral therapy, relaxation techniques, and acupuncture. Furthermore, the variability in IBS presentations leads to distinct treatment strategies tailored for constipation or diarrhea predominant IBS, as well as specific symptom management, particularly addressing abdominal pain. This research aims to investigate the potential pathophysiology of IBS by looking at the literature to investigate the potential theories. Furthermore, it will investigate

the current treatments for IBS and their effectiveness at treating the different subtypes of IBS.

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LIST OF ABBREVIATIONS

5-HT.....5-Hydroxytryptophan (Serotonin)

$5HT_3$..... Serotonin Type-3 Receptor

$5HT_4$..... Serotonin Type-4 Receptor

AIDS .....Advanced Immunodeficiency Syndrome

BU .....Boston University

CD4+ Cell .....T Helper Cell

CD8+ Cell .....Cytotoxic T Cell

FDA..... Food and Drug Administration

fMRI .....Functional Magnetic Resonance Imaging

FODMAP……...Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols

HIV ..... Human Immunodeficiency Virus

IBS ..... Irritable Bowel Syndrome

IBS-C .....Constipation Predominant IBS

IBS-D .....Diarrhea Predominant IBS

IBS-M..... Mixed IBS

IBS-U ..... Unspecified IBS

IEL.....Intraepithelial Leukocytes

IFN-χ.....Interferon Gamma

IgE..... Immunoglobulin E

IgG .....Immunoglobulin G

IL-1 ..... Interleukin-1

IL-10 ..... Interleukin-10

IL-12 ..... Interleukin-12

IL-2 ..... Interleukin-2

IL-6 ..... Interleukin-6

IL-8 ..... Interleukin-8

PEG ..... Polyethylene Glycol

PI-IBS ..... Post Infection Irritable Bowel Syndrome

SIBO ..... Small Intestine Bacterial Overgrowth

SSRI ..... Selective Serotonin Reuptake Inhibitor

TCA ..... Tricyclic Antidepressant

TGF-β ..... Transforming Growth Factor Beta

TNF-α ..... Tumor Necrosis Factor Alpha

INTRODUCTION

Irritable bowel syndrome, also known as IBS, is a common gastrointestinal disease that includes symptoms such as but not limited to chronic abdominal pain and discomfort and altered bowel habits. [2] These symptoms can greatly alter a patient's quality of life, with one study finding that on average 73 days a year are restricted because of symptoms such as pain, bowel difficulties, bloating, and dietary restrictions. [1] While IBS is thought to have a worldwide prevalence of ten to fifteen percent, the exact cause of IBS is not completely understood. [2] Many recent studies have attributed a few possible potential causes of symptoms such as dysregulation of gut motility, visceral hypersensitivity, inflammation, postinfectious symptoms, microbiome dysfunction, food sensitivity, genetics, and psychosocial dysfunction. [2]

Symptoms

The most common symptom of IBS is abdominal pain or discomfort. The associated symptoms of IBS can also range in severity between people, with some experiencing a mild case to some experience a debilitating severe version of the disease. According to Drossman et al., 2009, the factors that contribute to severity can range from most commonly pain to least commonly incontinence. These factors are summarized in Table 1 below. [1]

Table 1: Factors that Contribute to Severity, (N=1966)

(Adapted from Drossman et al., 2009)

Factors that make your IBS Severe	**N (%)**
Pain	1563 (79.5)
Bowel difficulties	1463 (74.4)
Bloating	1365 (69.4)
Limits eating/diet	1360 (69.2)
Limits social	1209 (61.5)
Cannot leave home	1051 (53.5)
Limits work/school	987 (50.2)
Limits thinking	975 (49.6)
Trouble sleeping	892 (45.4)
Nausea	830 (42.2)
Limits home acts	771 (39.2)
Poor QOL	766 (39.0)
Incontinence	537 (27.3)
Other troubles	212 (10.8)

As shown in Table 1, the symptoms experienced by over half of participants in the study were pain, bowel difficulties, bloating, limited diet, limited social activities, and inability to leave home. The study further revealed that the average respondent had to restrict their activity 73 days a year, which is 20% of

the calendar year. [1] This shows that IBS is a disease that is both unpredictable and severe enough to cause significant burden on the average person with the disease.

Diagnosis

The diagnosis of IBS is by association with the Rome criteria, updated frequently and currently on the fourth edition, Rome IV. The Rome IV criteria for diagnosis are summarized in Table 2.

Table 2: Summary of the Rome IV criteria for irritable bowel syndrome

Adapted from (Defrees et al., 2017) and (Oka et al., 2020)

Duration	Frequency	Symptoms
≥3 months of persistent symptoms with symptom onset at least 6 months before diagnosis	≥1 day per week	• Recurrent abdominal pain with at least 2 of the following criteria: ○ 1. Related to defecation ○ 2. Associated with change in frequency of stool ○ 3. Associated with change in form of stool

As noted in Table 2, the criteria for diagnosis include three months of persistent symptoms that have an onset at least six months before diagnosis along with an average of greater than one day a week. Furthermore, the

symptoms must include recurrent abdominal pain in association with two the following: relating to defecation, association with change in frequency of stool, and/or association with change in form of stool. [2,3]

Furthermore, IBS can be broken into four subtypes, IBS-D (diarrhea), IBS-C (constipation), IBS-M (mixed), and IBS-U (unspecified). Patients with IBS-D have at least 25% of their bowel movements as a Bristol Stool Form (BSF) scaled score of 6 or 7 and less than 25% are 1 or 2. Patients with IBS-C have greater than 25% BSF 1 or 2 and less than 25% are 6 or 7. Patients with IBS-M greater than 25% of bowel movements have a BSF of 1 or 2 and greater than 25% have 6 or 7. In IBS-U, the criteria for one of the previous cannot be met. [4]

It is important in patients who present with IBS symptoms, especially those relating to IBS-D, that other more serious conditions are ruled out. If patients present with diarrhea accompanied by weight loss, hematochezia, iron deficiency, abnormal complete blood cell count, abnormal comprehensive metabolic profile, or increased inflammatory markers, the American College of Gastroenterology Functional GI Disorders Task Force recommends further testing such as fecal leukocytes, testing for *Clostridium difficile*, obtaining travel history to check for parasitic infections, testing for tissue transglutaminase antibodies for celiac disease, and colonoscopy to screen for colon cancer, celiac disease, ulcerative colitis, and microscopic colitis. [5] Upon ruling out all of these, and satisfaction of the Rome IV criterion, a diagnosis of IBS can be confirmed, and treatment options should be discussed.

Potential Treatments

There are multiple different types of treatment options for the different subtypes of IBS depending on the symptoms the patient is experiencing. Furthermore, these treatments can be broken up into both pharmacological and nonpharmacological treatment options. The pharmacological treatments for three of the most common symptoms, diarrhea, constipation, and abdominal pain, will be summarized in the table below.

Table 3: Summary of typical pharmacological treatments for different IBS symptoms

Adapted from (Bonetto et al., 2021)

Symptom Alleviated	Mechanism of Drug	Drug Example
Diarrhea	Peripheral opioid agonist	Loperamide
Diarrhea	5-HT3 receptor antagonists	Alosetron
Diarrhea	Mixed opioid agonists/antagonists	Eluxadoline
Diarrhea	Antibiotics	Rifaximin
Constipation	Soluble fiber	Psyllium
Constipation	Laxatives	Polyethylene glycol
Constipation	Type 2 chloride-channel activator	Lubiprostone
Constipation	Guanylate cyclase-C agonist	Linaclotide
Abdominal Pain	Antispasmodics	Dicyclomine
Abdominal Pain	Tricyclic antidepressants	Desipramine
Abdominal Pain	Selective serotonin reuptake inhibitors	Paroxetine

These drugs are commonly prescribed by providers for the symptoms of diarrhea, constipation, and or abdominal pain. As noted by the table, different drugs with different pharmacological methods of action can relieve different symptoms. [4]

Furthermore, there are a few nonpharmacological suggested treatments to help alleviate symptoms, each with their own varying success rates. Studies have shown that improvement of symptoms have occurred from increasing dietary fiber, following a low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols), following a gluten free diet, and increasing exercise. [6] There are also alternative therapies that have shown to be somewhat effective such as prebiotics and probiotics and other herbal therapies. [6] There have also been limited clinical studies in the effectiveness of aloe vera supplementation. [7]

These dietary changes work by eliminating foods that may be one of the potential causes of symptoms while the supplementation works by having a similar effect as pharmacological intervention with differing mechanisms depending on the substance being taken. [7]

SPECIFIC AIMS

Irritable bowel syndrome is a chronic condition that affects up to 10 to 15 percent of Americans. [8] Currently, there is no cure for IBS, there is only pharmacological intervention for symptom management. IBS is also frequently a debilitating disease for many of the patients who have it. Research has shown that patients with IBS score less on a measure of physical, social, and emotional wellbeing than those without the disease. [9]

The goal of this thesis is to understand and compare the different treatments available for patients suffering from irritable bowel syndrome. Currently there are many different treatment options for IBS and the three subtypes: IBS-D (diarrhea prominent), IBS-C (constipation prominent), and IBS-M (mixed). This thesis will investigate both nonpharmacological and pharmacological treatments and determine which medications are most effective in patients regarding specific subtypes of IBS. This will be accomplished by discussing the current pharmacological treatments for the differing symptoms and their efficacy based on recent studies. This thesis will also investigate nonpharmacologic treatments such as supplemental treatments and dietary modifications and investigate their effectiveness. Furthermore, current treatments that are undergoing clinical trials will be discussed as well.

PATHOPHYSIOLOGY

There are many different ideas for how IBS produces its classical symptoms of abdominal discomfort and gastrointestinal disturbances (such as constipation or diarrhea). Some leading theories believe that these disturbances are caused by issues with the gut brain axis. [10] However, others believe that IBS is caused by organic disease within the gastrointestinal tract. [11] The five main theories, which this thesis will discuss, are post infection activation of IBS, serotonin dysregulation, bacterial overgrowth, brain-gut interaction, and genetic factors.

Post Infection Immune Response

A specific subset of IBS, PI-IBS (Post Infection Irritable Bowel Syndrome), is believed to be caused by a prolonged infection such as bacterial enteritis, protozoan, or helminth infections. [11] This prolonged inflammation can be seen with an increase of pro inflammation factors such as mast cells, IELs (intestinal intraepithelial T-type lymphocytes), and CD4+ and CD8+ lymphocytes. There is also an increase in paracellular permeability that can be seen. [12] This data can be seen in Figure 1 below.

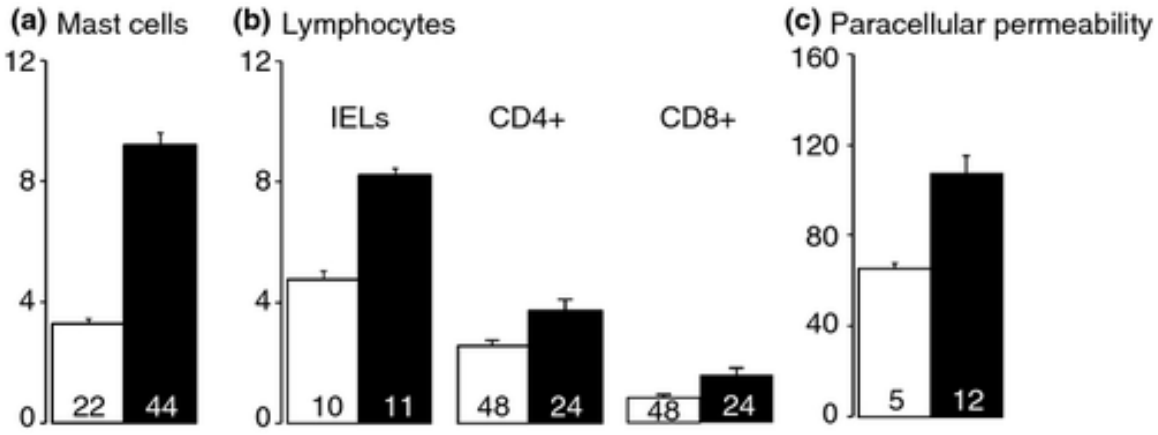


Figure 1: Altered immune activation and increased intestinal permeability in IBS patients Increased mast cells, lymphocytes, and paracellular permeability in IBS patients compared to control patients. Figure taken from (Matricon et al., 2012)

Figure 1 shows that there may indeed be an immune factor in IBS, and certain treatments are both available and being developed to target this potential cause. [12] It is also believed that the increased number of mast cells are involved with the permeability of the intestinal wall. A study was conducted showing that the enzyme tryptase, an enzyme found in mast cells, increased rectal permeability in IBS-D patients following exposure. [13] There were also studies conducted which measured the elimination of orally given sugars or radioisotopes by the kidneys that showed that IBS patients have increased permeability in the small intestines. [14-16]

Furthermore, inflammatory factors have also been measured in the guts of IBS patients, to mixed results. Different pro-inflammatory factors (IL-1, IL-2, IL-6, IL-8, IL-12, TNF-α or IFN-γ) have been shown to be either up-regulated or down-regulated in different studies. However, these studies all concluded that the anti-

inflammatory cytokines IL-10 and TGF-β were down-regulated in IBS patients. [12]

Finally, there have been multiple studies which investigated the protease activity of trypsin and thrombin in the colon. These proteases have antimicrobial properties and can contribute to inflammation of the colon via protease-activated receptors. The studies showed that the levels of trypsin and thrombin were increased in the colon of IBS patients. [17,18]

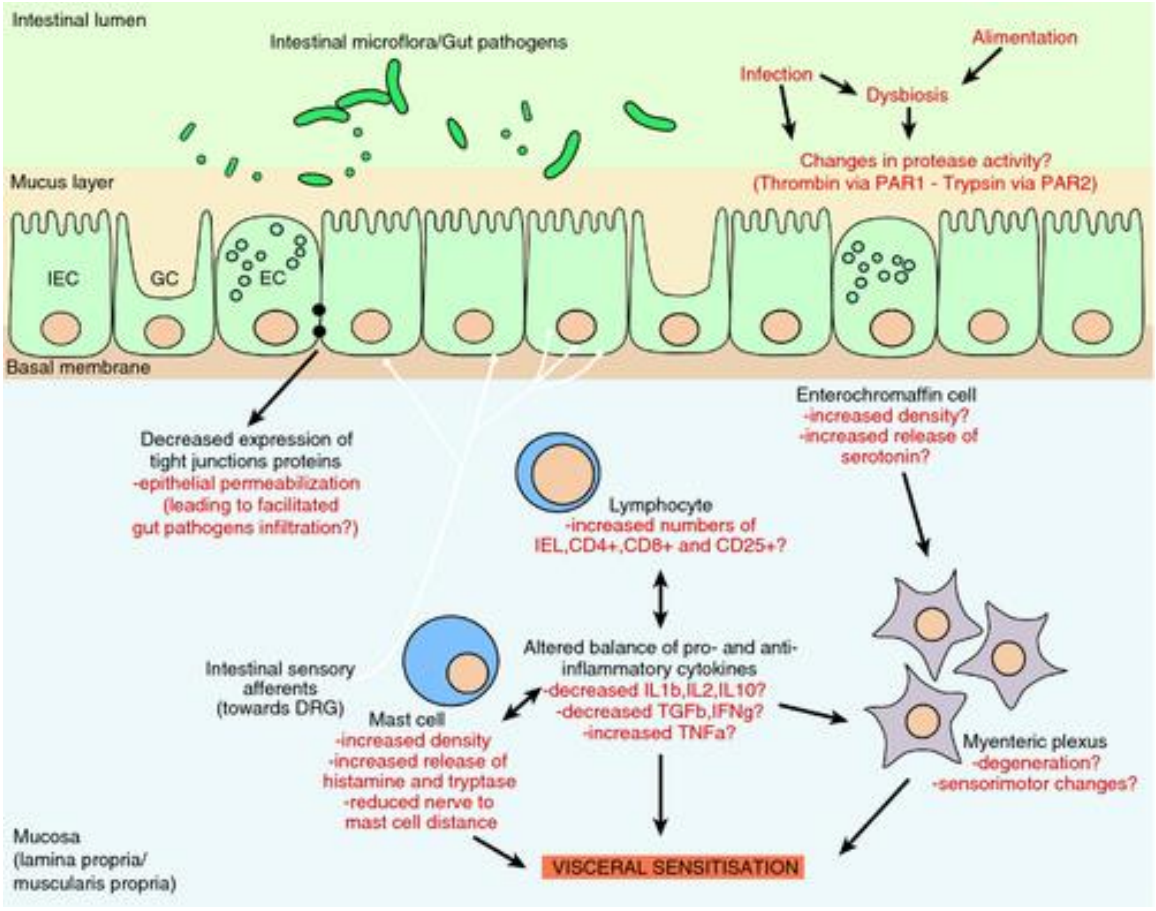


Figure 2: Summary of the potential pathophysiological mechanisms in IBS patients Multiple potential theories about how the visceral sensation experienced by IBS patients is brought about physiologically. Figure taken from (Matricon et al., 2012)

Figure 2 summarizes the potential mechanisms of pathophysiology discussed previously. In the intestinal lumen, pathogens could enter the epithelial layer through increased paracellular permeability. This would cause an immune reaction leading to increased mast cells and lymphocytes recruited to the area. These immune cells would then cause the dysregulation of different pro-inflammatory or anti-inflammatory cytokines such as the downregulation of anti-inflammatory IL-10 and TGF-β. Although there are many different theories about the activation of IBS in patients, many of these theories can be intertwined in a complete mechanism that leads to increased visceral sensation and causes the classical symptoms of IBS. [12]

Serotonin Dysregulation

Serotonin, or 5-hydroxytryptamine (5-HT), is a neurotransmitter that also functions as a hormone throughout the body. The intestines are the largest source of serotonin in the body, and over 90% of serotonin in the intestines are contained in enterochromaffin cells. Through specialty receptors in the gastrointestinal tract, serotonin is thought to play a specific role in gastrointestinal motility, sensation, and secretion. Two of these specific receptors, 5-HT_3 and 5-HT_4 have been studied as potential treatment sites for medication. [5]

When it comes to serotonin in patients with IBS, studies have shown that there may be signs of dysregulation of the neurotransmitter. One study showed that in patients with constipation predominant IBS, serotonin levels are lower than control patients. [5] This finding helps support the use of antidepressants

such as selective serotonin reuptake inhibitors (SSRIs) to help with the reduced concentration of plasma serotonin. Furthermore, another study concluded that patients with diarrhea predominant IBS have an increased plasma serotonin level. [19] This helps further support the use of 5-HT_3 and 5-HT_4 antagonists in patients with IBS-D. Although many of these drugs, which will be discussed in further detail later, have moderate to severe side effects, studies have shown that medications that act as antagonists to these receptors decrease secretion and visceral sensitivity, thereby controlling diarrhea and abdominal pain in patients. [12] On the contrary, 5-HT_3 and 5-HT_4 agonists have been shown to do the exact opposite, increasing secretion, and therefore causing more frequent bowel movements, potentially useful in the treatment of constipation predominant IBS. [20]

Bacterial Overgrowth

Small intestinal bacterial overgrowth, or SIBO, is a condition caused by excess bacteria within the small intestine. Symptoms can vary, but usually can include chronic diarrhea, malabsorption, unintentional weight loss, nutritional deficiencies, and osteoporosis. [21] SIBO is measured using hydrogen breath testing, in which a patient consumes lactulose, an indigestible carbohydrate, and the hydrogen produced by bacteria in the small intestine is measured. Studies so far regarding the connection between IBS and SIBO have produced mixed results, suggesting a connection is possible.

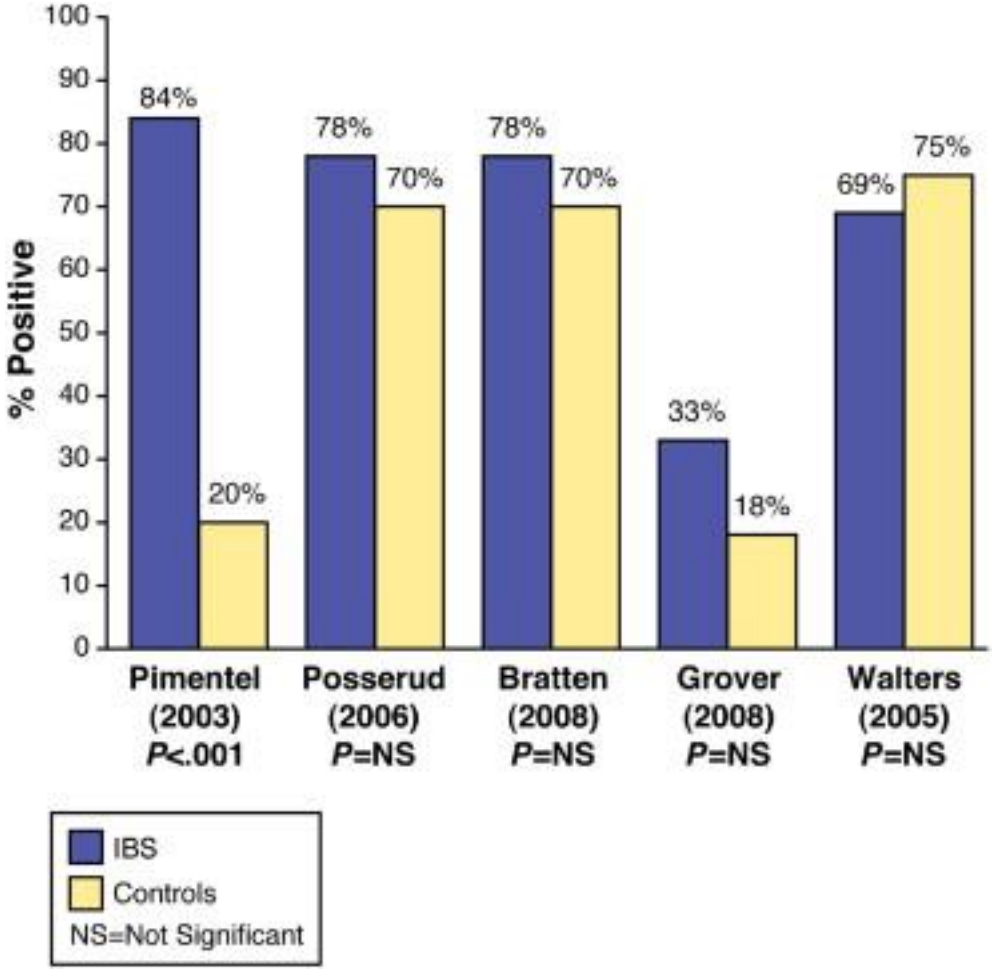


Figure 3: Differing studies comparing SIBO diagnosis in IBS vs control patients Studies have resulted in differing conclusions regarding the connection between SIBO and IBS, with some finding a correlation and others finding none. Figure taken from (Spiegel, 2011)

Figure 3 shows that there are differing results when it comes to connecting IBS and SIBO. Most studies, like the ones above, have found inconclusive data for a connection between the diseases, especially when the hypothesis of SIBO directly causing IBS is evaluated. [22]

One of the biggest pieces of evidence used by proponents of the SIBO causes IBS theory is positive result when hydrogen breath testing is used. However, a study conducted in which patients consumed a meal containing radioactive technetium and ten grams of lactulose. Scintigraphic scanning was used along with hydrogen breath testing to measure both colonic transit and breath hydrogen levels every ten minutes for three hours. The test used the traditional diagnostic level of greater than twenty parts per million of hydrogen gas being a positive diagnostic for SIBO. However, the study used scintigraphy to view whether the meal had transited to the caecum at the time of a positive result, and if so, they considered the combined scintigraphy and breath test as negative for SIBO. The study found that although 63% of patients had an abnormal breath test within three hours in 88% of these causes, there was meal within the caecum at the time of the positive test. Therefore, this test may not be as diagnostic for true SIBO as once believed, which further argues that there is not a correlation between SIBO and IBS. [23] The inconclusive nature of the studies done, along with the fact that the hydrogen breath test could potentially give a false positive if the meal has already transited to the caecum means that there needs to be more research into wither SIBO can be correlated with IBS in any way, especially determining if SIBO is a potential cause of IBS.

Gut-Brain Interaction and Dysregulation

One of the most common symptoms of IBS is abdominal pain and discomfort. In healthy patients, the typical digestive process does not create any

discomfort that can be perceived. However, in patients with IBS, it is thought that an altered perception of the normal digestive process is a potential cause of the pain and discomfort. [24]

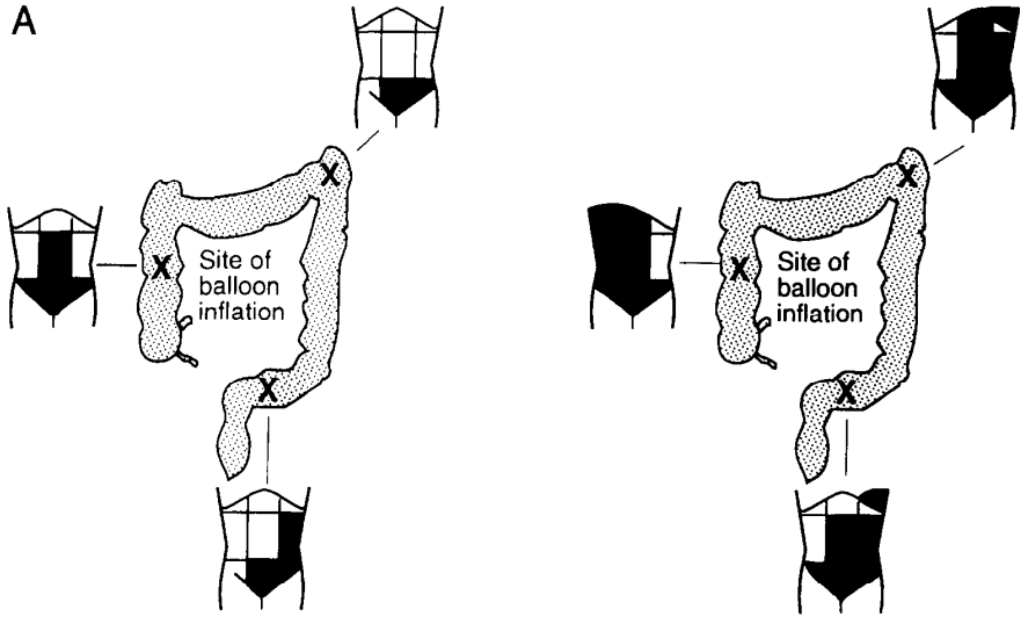


Figure 4: Balloon distension in different parts of the colon in healthy patients (left) and patients with IBS (right) The "X" marks the site where the balloon was inflated, and the black shaded regions mark where the patients experienced discomfort. Figure taken from (Mayer et al., 1994)

Figure 4 shows an experiment conducted in which a balloon was inserted into different parts of the colon and inflated, to which pain response was measured. The patients on the left, who were healthy, had a markedly lower response to the balloon distension than the patients on the right, who had IBS. It was hypothesized in the study that a potential cause for this difference is that in patients with IBS there is a hyperexcitability of the neurons in the dorsal horn, leading to abnormal responses of typically painless stimuli like normal digestion. [24]

Furthermore, studies have been done in which patients undergo a similar balloon distension within the digestive tract, and brain activity is measured using functional magnetic resonance imaging (fMRI). In one study, patients with IBS were compared with patients who have ulcerative colitis and control patients. The study used rectosigmoid distension across the three patient populations and compared the regional cerebral blood flow during the distension process. The regional cerebral blood flow was measured using radiolabeled water position emission tomography at the beginning, while patients anticipated, and during distension. The results of the study showed that although there are no statistically relevant differences between patients with ulcerative colitis and controls, when those two groups are compared to the IBS patients, there is an increased activation of the amygdala, rostroventral anterior cingulate cortex, and dorsomedial frontal cortical regions. When compared to the ulcerative colitis and control groups, IBS patients also had a decreased activation of the right lateral

frontal cortex, which activates the dorsal pons and periaqueductal gray, both of which play a role in pain inhibition. Therefore, according to the study, it seems that potentially this gut-brain dysfunction that causes some of the symptoms associated with IBS by greater activation of limbic and paralimbic circuits. [25]

There have been studies that have furthermore investigated this potential decreased ability to inhibit pain in IBS patients, and they discovered that although control patients are better able to activate endogenous pain inhibition areas, there are potential treatments to help IBS patients achieve this pain inhibition. For example, the tricyclic antidepressant amitriptyline has been studied for this reason, and research shows that there is a statistically relevant reduction of rectal pain versus placebo. During fMRI of IBS patients, it was shown that during rectal distension, IBS patients had a greater activation of the anterior cingulate cortex than controls, a part of the brain related to pain and emotion. However, when IBS patients were given amitriptyline, inhibition of pain was achieved, and by fMRI shown to be caused by activation of the right prefrontal cortex, right insula, and perigenual anterior cingulate cortex. [26]

Genetics

Many diseases that affect certain populations are investigated for a potential genetic link that may be causing the symptoms. A potential genetic contribution to the pathology of IBS has been investigated by different studies that attempt to portray IBS as a disorder that has a genetic component of which in the future may be able to be used as a screening tool for the disease.

In a study done of one hundred patients with IBS, researchers found out that 33% of the patients had a relative who had been diagnosed with IBS as well. This can be compared to the study finding that when matched with an age, gender, and socioeconomic control patient, only 2% of the pairs had IBS. This shows that there is a potential greater risk for developing IBS if a relative also has the disease. [27]

Another large-scale study done of patients in Olmsted County, Minnesota further solidified the potential for IBS having a genetic component. A survey was conducted of 892 patients, aged 30 to 64, who had reported abdominal pain or bowel related symptoms in the past. The patients were asked in the survey if they had a first degree relative or spouse who also had abdominal pain or bowel related symptoms within the past year. Of the 643 people who returned the survey, the researchers found the likelihood of having a first degree relative or spouse with abdominal pain or bowel related symptoms made the respondent 2.3 times more likely to have a diagnosis of IBS themselves. [28] Given that the study concluded that both having a relative or spouse with IBS increased the respondent's likelihood of having the disease themselves, and that a spouse would not share any genetic similarity with the respondent, this study showed there is both potential genetic and environmental factors that influence the likelihood developing the disease.

To attempt to prove a genetic relation to the development of IBS, two twin studies have been conducted. The first conducted in Sydney, Australia, consisted

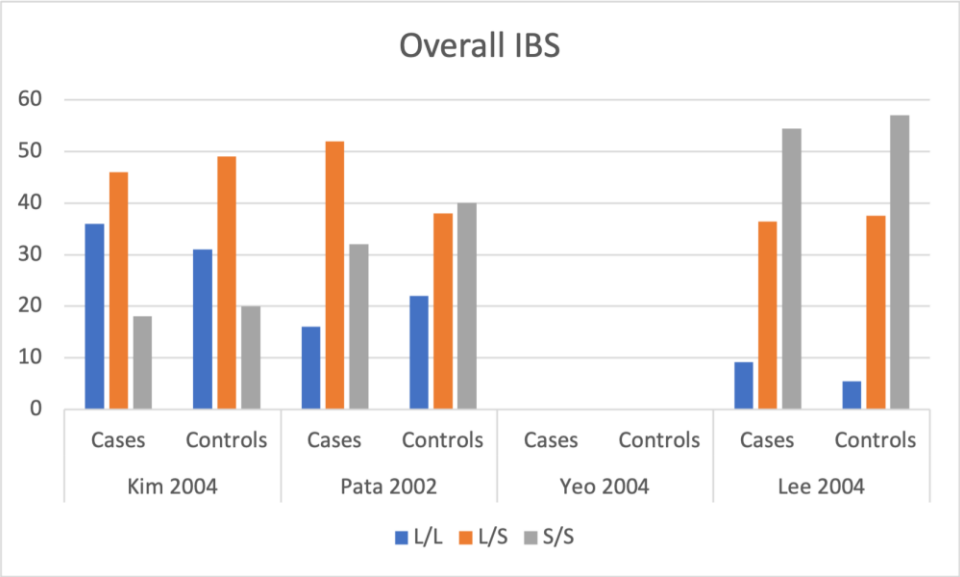
of 343 twin pairs of the same gender. This study concluded that monozygotic twins, who shared 100% of their DNA, had a greater concordance of IBS than dizygotic twins, who share only 50% of their DNA, at a rate of 33% for monozygotic versus 13% for dizygotic. This study concluded that the estimated genetic liability of IBS was 20%. [29]

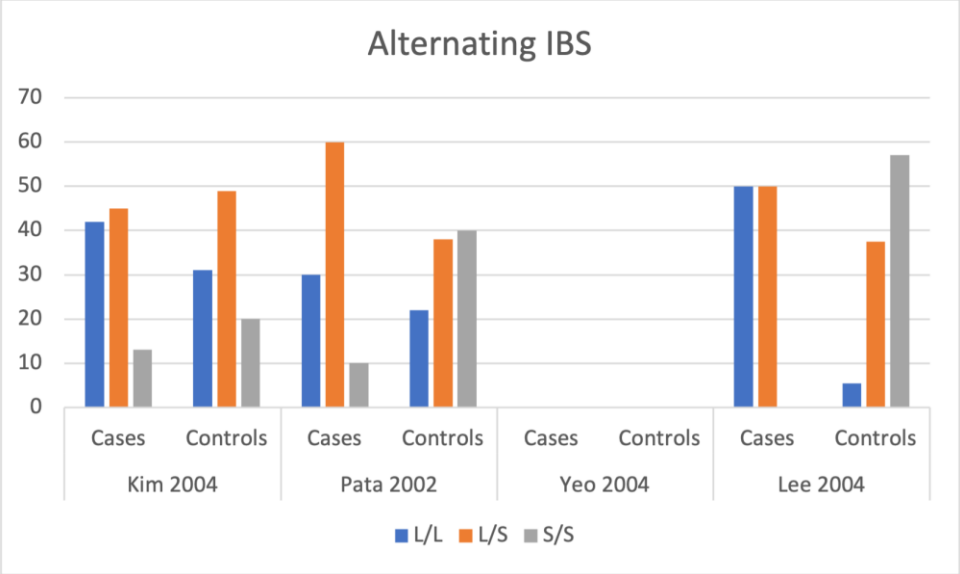
Another study of 6060 twin pairs in Virginia further proved the Australian studies results. The study concluded with similar results, with a concordance higher in monozygotic twins versus dizygotic twins at 17.2% to 8.4%, giving a genetic liability of 8.8%. In addition, the study also concluded that having a parent with IBS was of more predictive value than having a co-twin with IBS, with the study showing that 17.1% of monozygotic twins who had a mother with IBS developed the disease and 15.2% of dizygotic twins who had a mother with IBS developed the disease. [30]

As for what genes are thought to play a role, investigators have uncovered multiple hypotheses. Much of the investigation has been looking at genes that code for either the release of serotonin, serotonin receptors, or serotonin transporters because of serotonin's role in colonic motility. [31] One of the most important discoveries was an investigation into the promoter region of the serotonin transporter gene. The promoter region can code for two alleles which determine whether the transcribed serotonin transporter is either long or short. The short allele causes a serotonin transporter with lower efficiency, resulting in lower uptake of serotonin within the gut. Since serotonin plays a role in motility, it

was hypothesized that this would alter motility. It was shown experimentally in mice with the short allele that this allele caused accelerated colonic motility. [32, 33] This claim was further backed up when mice were given either tegaserod, a serotonin receptor agonist, or alosetron, a serotonin receptor antagonist. As predicted, the mice given tegaserod displayed increased colonic motility while the mice given alosetron experienced the opposite effect. [34, 35]

When investigated in humans, the serotonin transporter alleles produced mixed results. Four studies have been done that identified patients with either diagnosed diarrhea, constipation, or alternating IBS and controls who had their genotype analyzed for the serotonin transporter and compared the groups. The results of these four studies are shown in Figure 5 and described in further detail below.


Overall IBS
60
50
40
30
20
10
0
Cases
Controls
Cases
Controls
Cases
Controls
Cases
Controls
Kim 2004
Pata 2002
Yeo 2004
Lee 2004
L/L
L/S
S/S


Alternating IBS
70
60
50
40
30
20
10
0
Cases
Controls
Cases
Controls
Cases
Controls
Cases
Controls
Kim 2004
Pata 2002
Yeo 2004
Lee 2004
L/L
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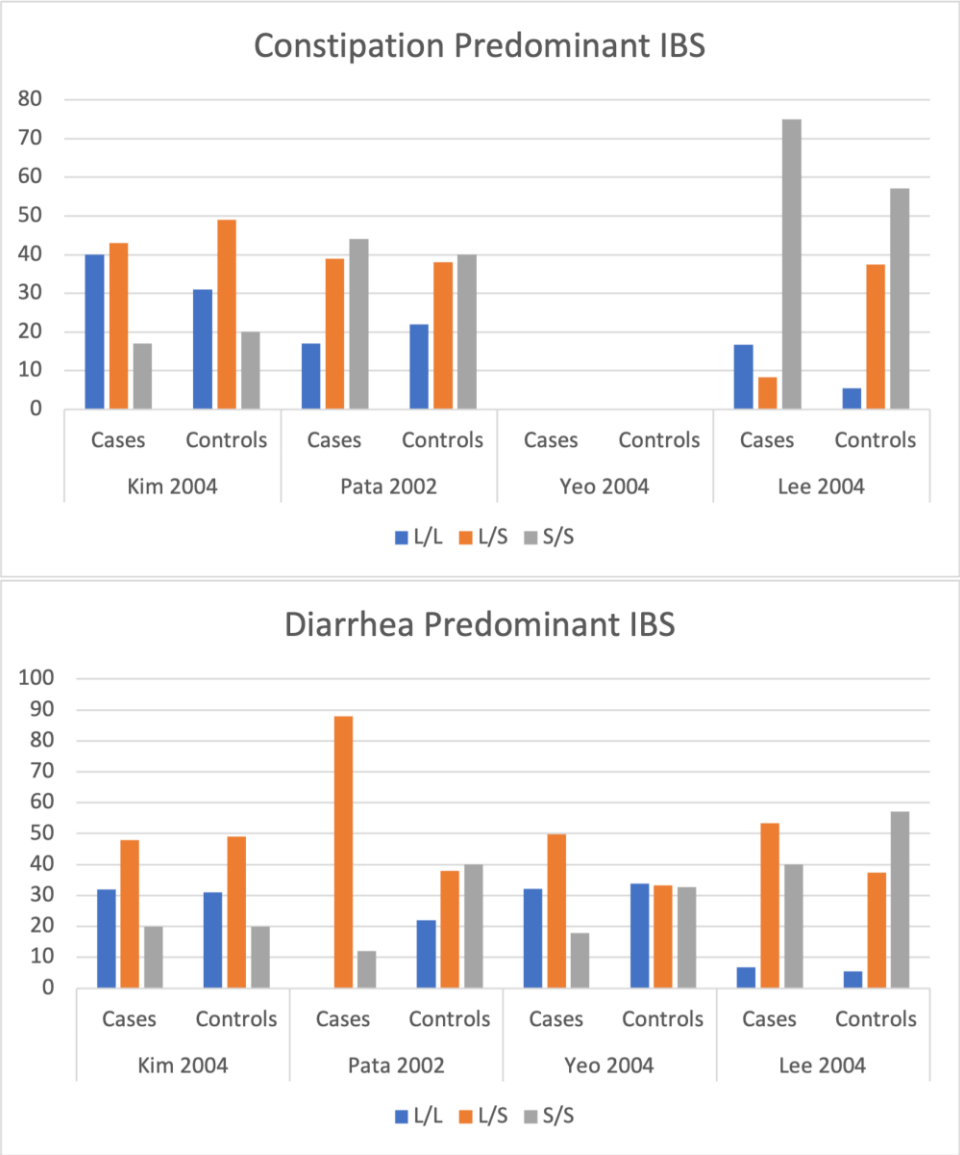

Figure 5: Genotype frequencies for the serotonin transporter in four different studies The different genotypes found in four studies, Kim, 2004; Pata, 2002; Yeo, 2004; and Lee, 2004, which produced results regarding the comparison of serotonin transporter genotype and IBS subtypes versus controls. Figure created with data from (Kim, 2004), (Pata, 2002), (Yeo, 2004), and (Lee, 2004).

As seen in Figure 5, Kim, 2004 found that those with the L/L (long/long) genotype were more likely to have constipation predominant IBS or alternating IBS than the L/S (long/short) or S/S (short/short) counterparts. [36] Pata, 2002 found that patients with diarrhea predominant IBS never had the L/L genotype, and that patients with the L/S genotype were statistically more common in the diarrhea predominant group versus the control group. [37] Yeo, 2004 found that those with the S/S genotype were more than twice as likely to be in the diarrhea predominant group versus the control group. [38] Finally, Lee, 2004 showed that despite promising evidence in previous studies, there was no evidence to support the matching of genotypes to a specific subset or IBS or the control group. [39] However, this study contained a small number of participants which may have affected results. Most importantly, however, is that these four studies were conducted in four different countries, and therefore may have had a race as a confounding variable not accounted for. [40]

NON-PHARMACOLOGICAL TREATMENTS

There are many differing theories into the effectiveness of non-pharmacological treatments for use in assisting with the treatment of IBS. The main topics regarding non-pharmacological treatments this thesis will explore in more detail are the impact of exercise, diet modification, FODMAP consumption, fiber intake, and probiotic supplementation.

The American College of Gastroenterology Task Force on IBS has not conclusively proven that hypnotherapy, cognitive behavioral therapy, relaxation techniques, and acupuncture are effective at treating IBS, but there has been emerging research on these topics. [41] A few studies have shown that there could be some potential effectiveness in relaxation techniques, hypnotherapy, and cognitive behavioral therapy which have shown a decrease in psychological distress, internal stressors, and gastrointestinal symptoms. [42-44] There have also been studies which investigated whether acupuncture is able to affect neurotransmitters such as serotonin, glutamine or acetylcholine release and reuptake. A few studies conducted in both animal and human patient populations have indicated that there is a coloration between specific acupuncture techniques and control of serotonergic, cholinergic, and glutamatergic pathways and blood cortisol levels. [45- 49] This goes to show that even though some treatments may not be considered conventional, there is still currently emerging research on new potential non-pharmacological interventions to assist with the treatment of IBS.

Exercise

Exercise has an impact on gastrointestinal motility and overall function by its effects on the central nervous system. Thus, multiple studies have been carried out to determine whether exercise could have a positive impact on those with IBS. One study compared both women with and without IBS to see the impact that exercise or lack thereof in their lifestyle may have on their symptoms. The study found that compared to the control women, women with IBS were less likely to maintain a lifestyle that included weekly moderate exercise than control women at 48% versus 71%. However, in the women who did participate in moderate weekly exercise, the study showed that there was a statistically smaller probability of certain symptoms such as the feeling of incomplete bowel evacuation and fatigue. However, general gastrointestinal upset was not different between the two groups. Thus, it was hypothesized by the authors that moderate weekly exercise may improve specific symptoms but not all symptoms in women with IBS. [50]

In another study done in a group of twenty-two males with diarrhea-predominant IBS, the role of exercise as a treatment was compared in one group versus another group which was taking the antidiarrheal loperamide. In the exercise group, yoga was preformed twice daily including a variety of yogic poses and specific breathing techniques. In the medication group, loperamide was taken once daily at a dose between 2-6 milligrams depending on the severity of symptoms. Both treatments were monitored with once monthly doctor's

appointments to assess current symptoms which was compared to the results of the pre-study symptoms of the participants along with electrogastrography and autonomic reactivity. At the end of the study, both groups had statistically similar improvement of overall symptoms, indicating that exercise had a similar effect as pharmacological treatment in this study. [51] Thus, it could be potentially effective to combine traditional pharmacological treatment with exercise to have a synergistic effect that leads to overall symptom improvement.

Diet Modification

Diet modification is an important factor in the nonpharmacological treatment of IBS. Many patients believe that certain foods or food groups are the main trigger of their symptoms, indicating what may be a food allergy. However, most often than not, symptoms are usually not caused by food allergies and rather it is the fact that a meal was just consumed that causes the initiation of IBS symptoms. [41]

This, however, does not mean that there are not certain foods that can trigger IBS symptoms more than others. A study conducted showed that patients are most likely to indicate the initiation of IBS symptoms after they consumed fatty foods, caffeine, alcoholic beverages, carbonated foods, or gas-producing foods such as beans, cabbage, and broccoli. [10] This food intolerance can usually be detected using an exclusion diet. The foods removed from the diet can vary, but most often include removing wheat, soy, fish, shellfish, tree nuts, peanuts, dairy, eggs, caffeine, potatoes, and citrus fruits. [52, 53] Even though

the removal of such a large amount of food groups can be difficult to follow, these elimination diets have been found to be very beneficial in certain cases. Thus, they seem to provide symptomatic relief in certain patients when done correctly and under supervision of a dietician and physician.

In a study done with patients with only diarrhea predominant IBS, approximately one third of patients experienced significant relief of symptoms by eliminating the aforementioned foods and slowly reintroducing them one by one to see which trigger their symptoms. [54] In a literature review conducted reviewing multiple studies of elimination diets, the percentage of patients who responded positively varied from 15% to 71%. [55] The patients who responded the best tended to suffer from diarrhea predominant IBS, while the most common trigger of symptoms was found to be milk, wheat, and eggs. Furthermore, one double blind, randomized, placebo-controlled study reported that in IBS patients who did not have celiac disease, removal of gluten from the diet had a significant improvement in quality of life, abdominal pain, bloating, stool consistency, and fatigue. [56] Therefore, patients who may test negative for celiac disease should consider adding gluten to their list for the elimination diet. Although there seems to be a reported positive benefit in elimination diets, especially in patients with diarrhea predominant IBS, an elimination diet is best done with the help of a dietician who has specific training in IBS specific elimination diets such that the risk of malnutrition is diminished since so many foods are being removed.

In addition to elimination diets in which all foods are removed, some elimination diets can be conducted with only specific foods with special testing. In a study consisting of patients who had not significantly improved with typical pharmacological intervention, IgE and IgG as well as mold panels were taken from each individual and those foods which elicited a result were eliminated from the diet. All participants in the study had at least one food item eliminated from their diet based on the panels results. The study showed that patients experienced a significant improvement after eliminating those foods and there was a statically significant improvement in stool frequency ($p < 0.05$), pain ($p < 0.05$), and quality of life score ($p < 0.0001$). When a one year follow up after the study was done, there was a continued adherence to the recommended diet, with patients saying they had minimal symptomatic problems and a perceived control over their IBS. [52] Overall, this could pose as a unique treatment that is tailored to each patient's needs with seemingly significant improvement in overall symptoms.

FODMAP Consumption

FODMAPs, or fermentable oligo-, di- and monosaccharides and polyols, have been a topic of recent investigation as a potential trigger for IBS symptoms. Many carbohydrates found in the typical diet are classified as FODMAPs like fructans, galactans, lactose, and fructose. FODMAPs also include sugar alcohols such as sorbitol, xylitol, and mannitol. [57] FODMAPs cause symptoms in certain patients by not being fully digested in the small intestine, leading to the sugar

entering the large intestine. In the large intestine, the sugar increases the osmotic load and is used as a substrate in bacterial fermentation leading to increased motility, diarrhea, and gas production. [58]

Fructans are long polymers of fructose with a singular glucose on the end. [58] Typically fructans are found in the diet come mostly from wheat and onions, and being that these fructans are completely undigestible, they provide a source of dietary fiber in our diet. [59] Fructans are the most well tolerated FODMAP in most people, as the typical fructan content in wheat containing foods and onion are too low to trigger symptoms. However, some foods, like leeks and Jerusalem artichokes are high sources of fructans and should be avoided by patients with IBS. [59]

Fructose is a monosaccharide that is typically found throughout the diet in honey, fruits, and as a component of table sugar. It is also found in high-fructose corn syrup which is added to many different foods such as soft drinks, bakery items, candy, and packaged snacks. [58] Fructose is best absorbed when paired in an equal amount with glucose, such in the case of table sugar (sucrose) and high-fructose corn syrup. [60] Specific fruits like strawberries and bananas also contain an equal amount of fructose and glucose and typically do not cause symptoms; however, fruits in which fructose is present in a larger ratio such as cherries, apples, and pears can typically lead to fructose malabsorption and activate IBS symptoms. [61] Similarly, fructose combined with the sugar alcohol sorbitol, another FODMAP itself, can cause the activation of IBS symptoms. [62]

Therefore, it is important for patients to be counseled on avoiding these foods if one is deemed to be trigger and educating them on other foods that may similarly cause problems.

Sugar alcohols, such as sorbitol, mannitol, xylitol, and erythritol are barely digested in the small intestine, and as such are typically added to sugar-free or reduced-sugar products to impart sweetness without the added caloric impact that typical sugars impart. They are a popular additive in food marketed towards diabetics as well since they do not affect blood sugar levels. [58] In a study done with otherwise healthy adults, ten grams of sorbitol was ingested by each participant with hydrogen breath samples, a sign of fermentation by bacteria rather than absorption, which can diagnose intolerance. Sorbitol intolerance was detected in 55% of nonwhite patients and 43% of the white patients tested, with severe incidence in 32% of the nonwhite patients, and 4% in the white patients. [63] This suggests that a potentially decent portion of the population has at least some sorbitol intolerance, and that further testing should be done in patients with IBS to see if these percentages are potentially higher than reported in this study.

Lactose, a disaccharide of galactose and glucose, is another problematic sugar that is found in dairy products. Lactose intolerance is one of the most common and well-known sugar intolerances in humans, so its role in aggravating IBS symptoms is a topic of much study. True lactose intolerance is a genetic disorder easily tested for, so a study was done in which the prevalence of lactose intolerance was compared between a group of patients with IBS and a group of

control patients. The study found that there was almost an equal rate of lactose intolerance in both the patients with IBS and the control patients. [64] Furthermore, another double-blind, placebo-controlled study showed that lactase supplementation, the enzyme that breaks down lactose in the small intestine and what is lacking in people with lactose intolerance, did not help reduce symptoms of IBS. [65] Interestingly, a study conducted showed that in IBS patients who removed cow's milk from their diet, whether they were lactose intolerant or not, showed that IBS symptoms may improve following this diet change, the mechanism of which is not clear and could potentially be drawn up to either organic or psychosocial factors. [66]

As the data has shown that each of the sugars within the FODMAP family can both aggravate symptoms of IBS when consumed and, when reduced or removed, help alleviate symptoms, studies have been conducted that aimed to show the benefit of removing all FODMAPs from the diet. One uncontrolled study showed that in IBS patients who had diagnosed fructose intolerance, removing FODMAPs from the diet resulted in symptomatic relief as expected since fructose is a FODMAP. [59] In another study a group of IBS patients were selected of whom had self-elected to consume a low FODMAP diet after their diagnosis. This double-blind and placebo-controlled study assigned each patient to a group of either high fructan, high fructose, high fructose and fructan, or high glucose (the placebo), and rotated each patient through each group throughout the duration of the trial. The patient continued their low FODMAP diet they were on before the

study; however, the patient drank a drink with each meal containing whichever sugar corresponded to the group they were assigned at that time. The results showed that symptoms were aggravated in 70%, 77%, 79%, and 15% of patients in the high fructan, high fructose, high fructan and fructose, and high glucose groups, respectively. [67] This study concluded that in approximately three fourths of patients, a low FODMAP diet could bring a potentially beneficial decrease in aggravation of IBS symptoms.

Another single-blind crossover study tested the production of hydrogen in the intestines via hydrogen breath test in both healthy controls and patients with IBS. Each patient was assigned to a group of either low FODMAP consumption or high FODMAP consumption for two days, at the conclusion of which the diet was switched and the tests rerun. A hydrogen breath test was conducted every hour for the final fourteen hours of each trial. The study showed that higher levels of hydrogen, which signaled incomplete digestion of sugars, was detected in both patients and volunteers in the high FODMAP trial than the low FODMAP trial. Furthermore, abdominal pain, increased bowel motility, flatulence, bloating, and lethargy were induced significantly in the patients with IBS who while in the high FODMAP trial. In the healthy controls, however, the only symptom experienced during the high FODMAP trial, was increased flatulence. [57] Overall, the data significantly supports the decrease of FODMAPs in the diets of those with IBS, even though a true FODMAP free diet may be difficult to follow with the typical American diet.

Fiber

Fiber supplementation has been a widely studied topic for its potential benefits in treating the symptoms of IBS. There are two types of fiber, and both have specific potential benefits upon supplementation. Soluble fiber, such as psyllium, fructo-oligosaccharides, oligosaccharides, and calcium polycarbophil are fibers that create a gel-like substance when dissolved in water. Insoluble fibers, such as wheat bran, corn bran, and flaxseed, do not dissolve in water, and maintain their original structure in the intestines. The potential benefits of these fibers are that soluble fiber helps with the bulking of stool, whereas insoluble fiber helps decrease colonic transit time, potentially helping with symptoms of IBS especially in those with constipation predominant IBS. [58]

Multiple comprehensive review studies have concluded that the benefits of fiber are either very limited or that supplementation should be used in patients with constitution predominant IBS only. [68, 69] The studies referenced in these comprehensive reviews, however, determined that between the two types of fiber, soluble fiber provided a much greater relief of IBS symptoms than insoluble fiber. [68, 69] A recent study conducted comparing the types of fiber tested Ispaghula husk, a soluble fiber, versus wheat bran, an insoluble fiber. The results of the study concluded that the Ispaghula husk was effective in alleviating the symptoms of constipation predominant IBS, whereas the wheat bran provided little to no effect on alleviating the same symptoms. [70] As opposed to supplementing by pill form, a few studies have also been conducted in which

patients were given either a high-fiber or low-fiber diet to follow to test the role of fiber from typical food. In each of the studies, in both the high-fiber and low-fiber groups IBS symptoms improved, and the studies concluded that there was a potential placebo or Hawthorne effect skewing the results. [71]

Another type of soluble fiber is a prebiotic which is a nutrient source for beneficial intestinal bacteria. One study sought to see whether the use of a partially hydrolyzed guar gum, a prebiotic, would be beneficial in alleviating IBS symptoms. The study concluded that the use of this prebiotic resulted in patients have decreased abdominal pain, but the prebiotic did not affect any other symptoms. [72] Another prebiotic, fructo-oligosaccharide, was investigated in a randomized, double-blind, placebo-controlled study which concluded that supplementation with fructo-oligosaccharide was beneficial for the reduction of abdominal pain, diarrhea, and constipation. [73] More research needs to be conducted in this relatively new field of supplementation with prebiotics to conclude on how effective they are in reducing IBS symptoms and in which subtypes of IBS they are most effective in.

Probiotics

Probiotics are live bacteria which are used as a supplement to help bolster the good bacteria living in the gut microbiome. Probiotics are found naturally in many fermented foods, such as yogurt and kimchi. It is believed that probiotics may help alleviate some of the symptoms of IBS. Two comprehensive reviews of previous probiotic studies concluded that there may in fact be potential benefits

to taking probiotics for IBS symptoms; however, many of the studies they reviewed used different strains and strengths of probiotics which made the studies difficult to adequately compare. [74, 75] Overall, while they may be beneficial, more studies need to be done comparing both the strain and strength of different probiotics, as well as their potential benefits on those with different subtypes of IBS.

PHARMACOLOGICAL TREATMENTS

Typically, if symptoms are severe enough and the patient is open to it, IBS is treated with pharmacological treatments as well as non-pharmacological treatments. Previously, many IBS pharmacological treatments focused on treating individual symptoms that the patient may be having rather than the entire condition. [11] For example, a patient with diarrhea predominant IBS may be prescribed medication specifically to treat their chronic diarrhea and another medication focused on helping with abdominal pain. However, with the development of many new medications that have shown promising results in treating multiple symptoms at once in all subtypes of IBS. [76] For the purpose of this thesis, specific focus will be given on both current medication and currently undergoing clinical trial medication for diarrhea predominant IBS, constipation predominant IBS, other therapies targeting specific individual symptoms.

Diarrhea Predominant IBS

One of the first line treatments in addressing diarrhea predominant IBS is loperamide, available over the counter and commonly known as Imodium. Loperamide is a μ-opioid agonist which works by binding to the μ-opioid receptor in the intestines and increasing colonic transit time, allowing for more reabsorption of water from the stool. [77] The downside to this treatment is that it both does not help with other IBS symptoms such as abdominal pain or stool frequency and that it is to be used “as needed”, therefore it is not preventing diarrhea only treating it. [78] While this may be a good treatment option for

patients who experience infrequent diarrhea as their primary complaint, many patients need to be prescribed one of the medications discussed below to achieve global symptom relief.

The use of tricyclic antidepressants, or TCAs, to treat diarrhea predominant irritable bowel syndrome were one of the first treatments that aimed to address all symptoms patients had rather than individual symptoms. When used in lower doses than would be used in treating depression, TCAs have been shown to definitively decrease abdominal pain, colonic transit time, and stool consistency. [79] TCAs work in treating abdominal pain in IBS patients by facilitating endogenous endorphin release, blocking norepinephrine release leading to inhabitation of pain pathways, and blocking releasing of serotonin which is part of the activation of the pain pathway. [80] TCAs are especially useful in the treatment of diarrhea predominant IBS because of their anticholinergic properties, the most of any antidepressant category, allowing for slowed intestinal motility. [81] Treatment with TCAs can be difficult to maintain for some patients due to the side effects associated with treatment such as sedation and anticholinergic side effects like constipation and dry mouth; however, with correct counseling of patients, this can prove to be a very beneficial treatment source with overall improved IBS symptoms. [82]

Alosetron, a serotonin 3-receptor antagonist, is a medication used to provide relief from common diarrhea predominant IBS symptoms by modulating the visceral afferent activity from the digestive tract. [83] Multiple clinical trials

have proven its efficacy in treating IBS symptoms such as abdominal pain, diarrhea, and stool frequency. Due to severe side effects like constipation and ischemic colitis, the drug was taken off the market and was reapproved by the FDA in a low dose formulation for females only. [84]

Rifaximin, a nonabsorbable antibiotic taken thrice daily for two weeks, has been studied in diarrhea predominant IBS for its potential benefit in both regular IBS patients and those who concurrently have small intestine bacterial overgrowth (SIBO). One study found that about 75% of patients with diarrhea predominant IBS also had abnormal lactulose hydrogen breath test results, signifying concurrent SIBO. The study further showed that in these patients, treatment with rifaximin both cured the SIBO and resulted in significant improvement in abdominal pain and diarrhea severity. [85] In patients without concurrent SIBO, trials have shown that treatment with rifaximin similarly resulted in successful improvement of IBS symptoms. [86] How rifaximin is helping treat the symptoms of IBS remains unclear, but a one-time two weeklong treatment can be an easy option for many patients who have diarrhea predominant IBS, although more studies need to be done to see how long the improvement of symptoms lasts.

Eluxadoline is a newer FDA approved medication that acts as a κ-opioid and μ-opioid receptor agonists and δ-opioid receptor antagonist. In its clinical trials, it showed that patients achieved improvement in both abdominal pain and stool consistency. Acting only on the enteric nervous system like loperamide, it

allows the decreased motility and deactivation of visceral afferent pain pathways of opioids without the central analgesic effects of other opioids. Eluxadoline does cause some severe side effects in patients without a gallbladder and those who consume multiple alcoholic beverages daily, and therefore it is contraindicated in those patients. [87] Otherwise, it provides significant symptom improvement in many patients, and furthermore, unlike loperamide, works in preventing symptoms as well as treating them when they occur.

Crofolmer is a medication, currently FDA approved for treating diarrhea caused by antiretroviral treatment in patients with HIV or AIDS, undergoing current clinical trials for its potential use as a medication in diarrhea predominant IBS. Derived from the *Croton lechleri* tree, it works by regulating the cystic fibrosis transmembrane conductance regulator and calcium-activated chloride channel, inhibiting secretion of chloride, and therefore decreasing the accompanying secretion of sodium and water. [88] In its Phase 2 clinical trial, the results concluded that in the women who participated, abdominal pain was reduced. The drug did not have any impact on stool consistency, however. The study concluded that it may have a future as a visceral analgesic for diarrhea predominant IBS. [89]

Constipation Predominant IBS

One of the first line treatments for constipation predominant IBS is polyethylene glycol (PEG) 3350, a laxative sold over the counter in many formulations such as the common laxative MiraLAX. As it only works as a

laxative, studies have found that PEG 3350 is only effective in improving stool consistency and stool frequency and is not effective in treating abdominal pain. [90] Consequently, PEG 3350 can be an effective treatment in those with constipation predominant IBS whose primary complaint is stool frequency and stool consistency, especially because of its ease of access as an over-the-counter medication.

Selective serotonin reuptake inhibitors, or SSRIs, are used as a treatment in constipation predominant IBS, specifically the SSRIs fluoxetine, citalopram, and paroxetine where each underwent clinical trials to investigate their efficacy in treating symptoms. Fluoxetine was shown to significantly improve abdominal pain, bloating, and stool consistency in patients after twelve weeks. [91] Citalopram and paroxetine were found to improve patient quality of life but did not significantly improve typical IBS symptoms such as abdominal pain, stool frequency, or stool consistency. [20, 92] SSRIs are thought to improve symptoms in constipation predominant IBS due to their ability to inhibit afferent pain pathways in the intestinal tract similarly to tricyclic antidepressants, but unlike the tricyclic antidepressants, they reduce colonic transit time leading to increased stool frequency. [11]

Lubiprostone is a locally acting chloride channel activator that enhances the chloride secretion of the cystic fibrosis transmembrane conductance regulator in the intestinal tract subsequently causing increased sodium secretion and, therefore, increased water secretion. Originally approved for those with chronic

idiopathic constipation, it has been approved by the FDA for females only with constipation predominant IBS. Clinical trials showed that lubiprostone improved patients' abdominal pain, bloating, constipation, and stool consistency. It also was shown to have very little adverse effects in comparison with placebo, the only one of statistical significance being nausea. [83] Overall, lubiprostone is a great treatment for females with constipation predominant IBS, with significant improvement in most symptoms. More studies should be conducted with males to see if it is similarly efficacious in them as well.

Linaclotide is a peptide that acts on the guanylate cyclase C receptor located on the surface of the epithelial cells in the intestine subsequently resulting in the secretion of chloride through the cystic fibrosis transmembrane conductance regulator and, therefore, sodium secretion and water secretion. In its phase 3 trials, linaclotide was shown to be effective in significantly reducing abdominal pain and improving stool frequency and consistency. Its only significant adverse effect was shown to be diarrhea in about one-fifth of study participants. [93] Unlike lubiprostone, linaclotide is FDA approved for both females and males, making it a good alternative for males looking to achieve significant improvement in their constipation predominant IBS symptoms.

Tenapanor is a selective inhibitor of the sodium-hydrogen antiporter in the epithelial cells of the intestines. By blocking sodium reabsorption, more water is secreted into the intestines. In its phase 3 clinical trial, it was shown to significantly improve abdominal pain, stool consistency, and stool frequency in

both males and females. The most common side effect was diarrhea and led to discontinuation in approximately 6.5% of the patients receiving tenapanor. Overall, tenapanor showed significant improvement in constipation predominant IBS symptoms, with few short-term and, as of now, no known long-term adverse effects. [94]

Tegaserod is a serotonin type-4 receptor agonist that improves constipation predominant IBS symptoms by increasing intestinal motility, therefore increasing stool frequency and improving stool consistency. Additionally, it was found to significantly improve abdominal pain in patients. [95] Unfortunately, tegaserod was withdrawn from the market in 2007 after the FDA associated it with potential adverse cardiovascular events in patients taking the medication. However, after multiple studies, it was reintroduced in 2018 with approval for treatment in females under sixty-five years of age. [96] Overall, tegaserod seems to be a beneficial medication at treating the symptoms of constipation predominant IBS, and with the results of future studies can potentially be used in male and elderly patients with similar beneficial results.

Elobixibat is a medication currently undergoing clinical trials for its potential use as a treatment in constipation predominant IBS. Elobixibat works by inhibiting the ileal bile acid transporter, causing bile acids to enter the large intestine where they increase colonic motility and decrease stool hardness. In its phase 2 studies, elobixibat was shown to increase stool frequency, improve stool consistency, and decrease abdominal pain. [97] Depending on the results of

ongoing phase 3 clinical trials, elobixibat may prove to be a beneficial medication in the overall improvement on constipation predominant IBS symptoms.

Other Symptom Targeting Therapies

One of the first treatments used specifically for abdominal pain associated with IBS were the antispasmodics class of medications. Medications in this class include dicyclomine and hyoscyamine and work by their anticholinergic effects on the intestinal tract resulting in less abdominal pain for the patient. [11] Studies regarding the effect of antispasmodics on the treatment of IBS have produced results that show that these medications are beneficial in treating abdominal pain for patients, but they show no benefit versus placebo for other common symptoms such as stool consistency and stool frequency. [98] Furthermore, these medications cause patients to experience many anticholinergic effects such as constipation, dry mouth, vision changes, and urinary retention, causing adherence to treatment to be difficult for some. [11] Additionally, some studies have shown that their use can cause tolerance in some individuals resulting in the medication not working as effectively in treating abdominal pain as well as previously. Therefore, it may be best for these medications to be used as an as-needed basis rather than daily on a prophylactic basis. [10] Nevertheless, these medications are prescribed by many clinicians as a first line therapy for IBS; however, some studies have additionally shown that the anticholinergic effect of constipation can exacerbate symptoms in those with constipation predominant IBS and should be used sparingly. [80]

Olorinab is a medication undergoing clinical trials for the treatment of abdominal pain in patients with both constipation predominant and diarrhea predominant IBS. It works by behaving as an agonist of the cannabinoid receptor 2 in the peripheral nervous system. In its phase 2b clinical trial, it was shown to provide significant improvement of abdominal pain at the largest dose tested in those who ranked their baseline abdominal pain as moderate to severe. All other doses and those with less than moderate baseline rated abdominal pain did not show significant improvement over placebo. [99] Overall, olorinab could potentially provide relief in patients with both subtypes of IBS whose pain is severe enough to cause interference in their daily life.

Another medication undergoing clinical trials, blautix, is a live biotherapeutic product containing a specific strain of the *Blautia hydrogenotrophica* bacteria. In its phase 2 clinical trials, both patients with constipation predominant and diarrhea predominant IBS were given treatment or placebo for eight weeks. The results showed that both patients with constipation predominant and diarrhea predominant IBS showed improvement in stool frequency and stool consistency. Furthermore, a significant improvement in abdominal pain was observed, and there were no significant adverse events when compared to placebo. [100] The results of this study showed that blautix could prove to be a safe and effective treatment in patients of both subtypes of IBS improving their stool frequency, stool consistency, and abdominal pain.

CONCLUSION

IBS can affect patients with a myriad of symptoms ranging from abdominal pain, altered stool frequency, altered stool consistency, and bloating. IBS is diagnosed based on the Rome IV criteria, which defines the duration, frequency, and symptoms required for diagnosis. [2] These symptoms can have an impact on patients' daily life, sometimes being debilitating enough to greatly restrict their typical day. The quality of life of patients with IBS is something ranked consistently lower than controls without the disease. [1] Thus, the search for both the cause of IBS and potential treatment options is of utmost importance for the advancement of treatment and subsequent relief for patients with the disease.

The pathophysiology for IBS is a heavily researched topic, with five leading theories: post infection immune response, serotonin dysregulation, bacterial overgrowth, brain-gut interaction, and genetic factors. The post-infection immune response is thought to be caused in a specific subset of patients due to prolonged inflammation after infection, and current research supports this theory for these patients. [12] Serotonin dysregulation is thought to be the reason for altered stool consistency in patients with IBS, with many treatments aiming to target the serotonin receptors in the intestinal tract. [12, 20] Bacterial overgrowth is a potential cause that the research is conflicting on, and therefore more studies need to be done regarding the topic. [22] Gut-brain interaction and dysregulation is a similarly heavily researched topic that has a lot of evidence supporting its role in IBS pathophysiology, especially in causing the abdominal pain that

patients experience. [24] Finally, genetics has been shown through research to play a main role in IBS, with twin studies showing that identical twins are more likely to both have IBS than fraternal twins. [30] Overall, research heavily supports post-infection immune response, serotonin dysregulation, gut-brain interaction, and genetics as having an important role in the pathophysiology of IBS, while bacterial overgrowth needs to be researched more to determine if it plays an important role.

Nonpharmacological treatments are employed by many patients with IBS, with the most researched being exercise, diet modification, FODMAP consumption, fiber intake, and probiotic supplementation. However, some research has been done on the potential benefit of hypnotherapy, cognitive behavioral therapy, relaxation techniques, and acupuncture with some success, and these topics should be studied in more detail to see if they can provide an improvement for IBS patients. [41] Exercise has been shown to have a positive impact on gastrointestinal motility and improving IBS symptoms. [50] Diet modification has been shown to positively impact patients as well, with many patients able to remove their “trigger” foods to much success. [55] One potential diet modification, the removal of FODMAPs, or fermentable oligo-, di- and monosaccharides and polyols, has been a topic of many studies comparing its benefit for those with IBS. Studies have overwhelmingly shown that the removal of FODMAPs from the diet improved IBS symptoms, potentially showing that these sugars are an activator of many patients’ IBS symptoms. [67] Increased

fiber intake has been shown to not particularly help those with IBS, with some limited improvement in those with constipation predominant IBS. [68] However, a type of soluble fiber called a prebiotic, has been the topic of recent studies with promising results as to its effectiveness, and more studies need to be conducted on its potential benefit for patients' symptoms. [73] Similarly, probiotics have shown some promising results, but the lack of studies comparing the efficacy of similar strain and strength probiotics limits the current comparative efficacy to other treatments. [74] Therefore, more studies should be done on probiotics to see if they can have a positive impact on patients' symptoms.

Treatments for IBS differ depending on whether they are targeted therapies for constipation or diarrhea predominant IBS or for specific symptoms such as abdominal pain. For diarrhea predominant IBS, μ-opioid agonists have been shown to work very well at reducing stool frequency and improving stool consistency, while mixed opioid agonists can also improve abdominal pain. [77, 87] Tricyclic antidepressants have been shown to help treat a lot of symptoms in diarrhea predominant IBS; however, the side effects have caused discontinuation in some patients. [79] Serotonin antagonists have also been shown to be helpful for the treatment of diarrhea and improvement of abdominal pain, stool frequency and stool consistency. [84] Nonabsorbable antibiotic therapy has been shown to provide benefit in some patients with diarrhea predominant IBS who also concurrently have small intestine bacterial overgrowth. [85] Finally, new

treatments for diarrhea predominant IBS show promising results, working by blocking the chloride secretion in the large intestines. [88]

For constipation predominant IBS, over the counter treatments such as laxatives have been shown to increase stool frequency and improve stool consistency; however, they have not been shown to improve abdominal pain. [90] Selective serotonin reuptake inhibitors have shown mixed results depending on the specific one used, but with some benefit to patients, and more studies should be done on these medications for their potential use in treating constipation predominant IBS symptoms. [91, 92] Medications that act as chloride channel activators or sodium channel inhibitors have been shown to significantly improve stool consistency, stool frequency, and abdominal pain in patients. [83, 93, 94] Serotonin agonists have also been shown to improve stool frequency and stool consistency, although their potential side effects have left them heavily regulated, and more studies should be conducted to see the long-term effects of these medications. [96] Finally, ileal bile acid transporter inhibitors are currently undergoing clinical trials for their potential use in improving abdominal pain and improving stool frequency and consistency. [97]

For abdominal pain, antispasmodics have been frequently used as a first line therapy; however, comparative studies should be done to see if they are more effective than other treatments that target abdominal and other symptoms of IBS. Cannabinoid receptor agonists and live biotherapeutic products are

currently undergoing clinical trials for the treatment of abdominal pain in IBS, with promising results as well. [99, 100]

Overall, the pathophysiology and potential treatments for IBS are well studied, but more studies need to be conducted. Potential further studies include seeing if specific subtypes of IBS are more influenced by different potential pathophysiologies and doing comparative studies on different treatments for IBS to see which is more beneficial for patients who have the same subtype of IBS. IBS research is certain to be a well-versed topic of the future, and because of this, many potential new treatments, or potentially even a cure, could be found quite soon.

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