The Link Between the Gut Microbiome, Mental Health, and IBD

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Chapter 1: An Introduction to the Gut-Brain Axis

"Gut health" is one of the latest trends to hit the internet. Aesthetically pleasing posts on Instagram and Tik Tok guide readers through "healing your gut microbiome" and hails it as a cure-all. Social media influencers tout apple cider vinegar shots and gluten-free diets to achieve it all: clearer skin, weight loss, and a better life.

To the scientifically educated these claims create a justifiable amount of skepticism. While lifestyle changes can certainly positively impact overall health, it is not as simple as consuming green tea and eight glasses of water a day. However, this trend has prompted an interesting conversation and debate surrounding the symbiotic interaction between our gut health and the rest of our body. Recent research advances are particularly focused on the growing importance of the gut-brain axis (GBA)- the bidirectional relationship that is present between the enteric and central nervous system.

The central nervous system (CNS) consists of the brain and the spinal cord and is divided into grey matter and white matter. The grey matter in the brain is present in the outermost layer and contains neuronal cell bodies and dendrites in addition to glial cells and capillaries. White matter refers to areas of the CNS where myelinated axons are located. Myelin is an insulating material that forms around axons and aids in the transmission of nerve signals.

Each hemisphere of the brain is divided into four lobes: frontal, parietal, temporal, and occipital. Each area of the brain is associated with different functions. The lobes are divided by gyri and sulci, bumps and grooves that increase the surface area of the brain and allow more brain matter to fit in the skull. The frontal lobe is responsible for advanced executive functioning. The frontal lobe is responsible for emotional regulation, planning, reasoning, and problem solving (Catani 2019). The parietal lobe is located behind the frontal lobe and is

responsible for integrating sensory information like touch, temperature, pain, and pressure (Dieterich & Brandt 2018). The temporal lobe contains areas that control the processing sensory information like language, hearing, and is responsible for forming memories (Friederici 2011). Finally, the occipital lobe is the brain's visual processing center (Marek & Dosenbach 2019).

The enteric nervous system (ENS) is a part of the autonomic nervous system that holds neural circuits that control motor functions, local blood flow, mucosal transport, and secrete acetylcholine and neuropeptides (Nezami & Srinivasan 2013). The ENS is comprised of primary afferent neurons that are sensitive to both chemical and mechanical stimuli, interneurons, and motor neurons. All these neurons act on smooth muscle, pacemaker cells, blood vessels, mucosal glands, and epithelial cells. It also is responsible for modulating immune and endocrine function (Costa et al. 2000). ENS dysfunction is commonly linked to digestive disorders, and its role in neurological and psychiatric disorders is becoming more apparent with advancing research (Heiss & Olofsson 2019).

The GBA involves interactions between the sympathetic and parasympathetic parts of the autonomic nervous system (ANS). This interaction connects the afferent and efferent signals between the gut and the brain. It also involves communication between the endocrine system, immune system, and autonomic nervous system (Agirman et al. 2021). The endocrine-neuro-immune mediators of the GBA play a large role in the brain's ability to affect the function of the intestines. Immune cells, epithelial cells, enteric neurons, and smooth muscle cells are all affected by these interactions. Additionally, the gut microbiome plays a massive role in the composition of the GBA.

An introduction to the basic anatomy of neuroanatomy, the ENS, and the CNS aids in understanding the more complex topic of gut-brain signaling. Though the GBA is still a

developing area of research, there has been much research laying the groundwork for expansion of our understanding in how the gut and brain interact.

Chapter 2: The Gut Microbiome and Gut-Brain Signaling

The human microbiome is defined as all the microorganisms on and in a host and its host's genetic material. The human microbiome has extensive functions such as the development of immunity, defense against pathogens and host nutrition. Host nutrition involves the production of short-chain fatty acids that are important in host energy metabolism. It also includes the synthesis of vitamins and fat storage. All these different functions have a major influence on human behavior. The human microbiome as an estimated 100 trillion microbes, the bulk of which live in our gut (Schmidt et al. 2018).

The human microbiome is composed of a community of microorganisms (bacteria, fungi, viruses) that have a greater complexity than the human genome itself. Because of the microbiome's size, the Human Microbiome Project (HMP) was established by the National Institutes of Health common fund in 2008 to understand the relationship between health and the human microbiome. The HMP has utilized a largely high throughput approach, incorporating sensitive omics technologies (proteomics, genomics) and analyses to characterize the human microbiome in health and disease (Cresci & Bawden 2015). Specifically, the human gut microbiome is being intensively studied for its putative effects on metabolism, immune responses, and behavior.

The gut microbiome is composed of microorganisms such as bacteria, archaea, fungi, and viruses throughout the entire gastrointestinal (GI) tract. A typical, healthy individual has trillions of microbes in their gut microbiome. However, no two microbiomes are alike. Research has

shown that several factors can impact the composition and overall health of the gut microbiome. Diet, medications, geography, lifestyle stage, the birthing process, infant feeding method, and stress (exercise, metabolic, psychological) have all been demonstrated to play critical roles (Cresci & Bawden 2015).

In the gut, the bacteria phyla Firmicutes and Bacteroides make up about 75% of the gut microbiota and are extremely sensitive to any changes (Pittayanol et al. 2019). Additionally, the rise in allergies, autoimmune diseases, metabolic disorders, and neuropsychiatric disorders are disrupters of the gut microbiome.

The gut microbiome interacts with the CNS through a few pathways. First, there is interaction through the vagus nerve. The afferent spinal and vagal sensory neurons carry information from the intestines to the brain stem. This engages the hypothalamus and limbic system, which are integral in regulating human emotions. The descending projections from the limbic system that are activated by stress, influence the autonomic activity in the gut (Dicks et al. 2021).

There is an emerging role for a bidirectional communication between the gut microbiome and neuroendocrine signaling. This interaction occurs through the stimulation of enteroendocrine cells (EECs) by bacterial products. This stimulation releases important neuropeptides such as neuropeptide Y (NPY), peptide YY, cholecystokinin, glucagon-like peptide-1 and -2, and substance P which all play roles in various physiological and homeostatic processes such as feeding, stress, anxiety, and pain amongst others. (Asadi et al. 2022; Foster et al. 2021).

The gut microbiome plays a critical role in the metabolism of several essential amino acids such as tryptophan as a precursor for the synthesis serotonin. An estimated 95% of serotonin (5-HT) is produced by enterochromaffin cells in the gut mucosa. 5-HT plays multiple

roles in the gut including GI pain perception, motility, and GI secretion. In the brain, 5-HT is involved in regulating mood and cognitive processes (Gao et al. 2020).

The gut microbiome also exhibits a bidirectional relationship with the immune system. The gut-associated lymphoid tissue makes up 70% of the immune system and is estimated to be the largest mass of lymphoid tissue in the body. Some components of the immune system include cytokines like (IL)-1B, IL-6, and tumor necrosis factor (TNF). These cells aid in the inflammation response of the immune system and generally help control immune cell activity and growth (Parkin & Cohen 2001).

Chronic stress has also been implicated in affecting intestinal permeability, a condition known as leaky gut syndrome. Leaky gut syndrome can induce an inflammatory response, and considering the bidirectional relationship of the GBA, has been hypothesized to be associated with psychiatric disorders. With a leaky gut, there are elevated levels of bacterial endotoxins called lipopolysaccharides (LPS) which are risk factors for disease. Other research has also explored the possibility that gut microbiota can influence neuropsychiatric disorders through the gut's production of neuroactive substances. This theory would implicate the gut microbiota in the pathophysiology of a host of psychiatric disorders, such as anxiety, depression, and autism (Obrenovich 2018).

Gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the brain, is produced by many species of Lactobacillus and Bifidobacterium. Additionally, the bacteria Candida, Enterococcus, and Escherichia produce serotonin, and some Bacillus produce dopamine. Bacteria also produce short-chain fatty acids (SCFAs) like butyric acid, propionic acid, and acetic acid. These fatty acids stimulate the sympathetic nervous system and mucosal

serotonin release. Subsequently, the memory and learning process in the brain is influenced (Yunes et al. 2016).

Chronic stress can have severe negative effects on the human gut microbiome. When there are increased levels of cortisol, the permeability of the gut wall increases. This causes leaky gut, which induces an inflammatory response in the body. A leaky gut's is reflected by increased levels of proinflammatory cytokines including TNF-α, interferon-y, and IL-6. IL-6 activates the HPA axis and down-regulates glucocorticoid receptors. Activation of the glucocorticoid receptors are part of a feedback mechanism that suppresses the HPA axis. However, this inflammation related downregulation only results in a hyperactive and overly sensitized HPA axis. Stress-related gut changes like leaky gut can also reduce the hippocampal serotonin and reduce brain-derived neurotrophic factor (BDNF) expression.

With an understanding of the basis for the GBA, it is important to also examine how gastrointestinal disorders can alter both brain and GI function due to the clear connection between the brain and the gut.

Chapter 3: Irritable Bowel Disease

Irritable Bowel Disease (IBD) refers to Crohn's Disease and Ulcerative Colitis. These diseases are characterized by chronic inflammation of the gastrointestinal tract (GI tract), which can damage it over time. While Ulcerative Colitis is inflammation in the large intestine and rectum alone, Crohn's Disease can affect any part of the GI tract *(*Yangyang & Rodriguez 2017). Crohn's Disease is most seen in the small intestine. In Ulcerative Colitis, the inflamed damaged areas are continuous, starting at the rectum and spreading into the colon. However, in Crohn's the damaged areas are "patchy" and can affect multiple discontinuous areas of the GI tract and

neighbor healthy tissue. Inflammation in Colitis is found only in the innermost layer of the colon's lining whereas inflammation in Crohn's reaches through multiple layers of the GI tract walls (Zhang & Yu Li 2014).

Common symptoms of IBD include persistent diarrhea, abdominal pain, rectal bleeding, bloody stool, weight loss, and fatigue. While IBD's exact cause remains unknown, there are a few theories as to its causes. The first theory is that the immune system is incorrectly responding to triggers like a virus or bacteria which causes inflammation. The second cause is likely related to genetics, as those with a family history of IBD are more likely to develop this incorrect immune response (Zhang & Yu Li 2014).

IBD is diagnosed with different tests such as endoscopy, colonoscopy, contrast radiography, magnetic resonance imaging, computer tomography, stool samples, and blood tests. IBD has a few possible treatment routes, such as 5-aminosalicylic acids, immunomodulators, corticosteroids, and biologics. In extreme cases, patients undergo surgery to remove overly damaged parts of the intestines *(*Yangyang & Rodriguez 2017).

While IBD was once thought of as a disease plaguing Western civilization, it is now being seen in globally developing countries in Asia, Africa, and South America. Rates of IBD, though high in Western countries, are stabilizing. However, the age of onset continues to decrease worldwide. In newly developed countries, IBD seems to be rapidly increasing, burdening the delicate healthcare infrastructure (Windsor & Kaplan 2019).

The mechanism of inflammation is due to interactions between the mucosal immune system and the microenvironment. Luminal antigens, T lymphocytes, intestinal epithelial cells, cells that belong to the innate and adaptive immune systems, and secreted mediators all contribute to sustained inflammation in genetically predisposed IBD patients. Northern

American and European people are especially at risk for IBD (Ananthakrishnan 2015). People with first-degree relatives with IBD are especially at risk, and genetically isolated groups like Ashkenazi Jews carry the highest risk of disease (Oostenbrug et al. 2003). Along with genetics, environmental and lifestyle factors like smoking, obesity, physical inactivity, and a western-style diet are considered one of the biggest risk factors in the development of IBD (Piovani et al. 2019). Additionally, bacterial flora is implicated in the development of IBD and higher levels of mucosal antibodies against intestinal bacteria have been seen in patients with IBD (Hyon & Mayer 2006).

IBD is a complicated and systemic inflammatory disorder without any known cure. With an understanding of the gut's role in overall health, it is worth examining the implications of a gut-focused inflammatory illness and its effects on the entire body.

Chapter 4: The Serotonergic System and Mental Health

The serotonergic system is hypothesized to play a foundational role in both the cause and treatment of many psychiatric disorders. Serotonin, also known as 5-hydroxytryptamine, is a signaling molecule that plays a fundamental role in many physiological systems Neurons that use serotonin as a primary neurotransmitter within the nervous system are mostly found in the brainstem on the midline raphe nuclei and extend down into the subnuclei of the lateral reticular formation. There are two types of serotonergic neurons the first are a rostral group that is in the midbrain and rostral pons. This group has a projection to the forebrain. Then, there is a casual group that is found in the caudal pons and the medulla that projects to the spinal cord. Both the caudal and the rostral group project to the brainstem (Hall, 2013).

Serotonin is synthesized in the serotonergic neurons of the central nervous system and the enterochromaffin cells of the gastrointestinal tract. It is synthesized from the essential amino acid tryptophan, which is then converted to serotonin following a series of biochemical reactions. About 95% of serotonin is synthesized and stored in the gastrointestinal enterochromaffin cells and the remaining 5% is produced and stored in the brain-stem neurons (Jonnakuty & Gragnoli, 2008; Mercado et al. 2022; O'Mahony et al. 2015).

Due to the widespread presence of serotonin receptors in the human body, there are many physiological systems in which serotonin is involved. Seven different types of serotonin receptors exist, which are classified according to structure, transduction signal, and pharmacology. Serotonin has a known role in platelet aggregation, and regulation of smooth muscle in the gastrointestinal and cardiovascular system and plays a role in mood disorders like depression and anxiety neurons (Mercado et al. 2022).

Serotonin's role in psychiatric disorders has been long studied. It is thought to play a role in depression, anxiety, obsessive-compulsive disorder, eating disorders, and addiction (O'Mahony et al. 2015). The hypothesis regarding serotonin's role in clinical depression has existed for about 50 years. However, it is still widely debated. Significantly, one of the mainstream treatments for depression, SSRIs, isn't effective in all patients with depression, indicating that there are factors at play beyond serotonin disruption in chronic depression (Murphy et al. 2021).

In a study by researchers Lam et al. (1996), individuals with major depressive disorder showed low levels of tryptophan, the essential amino acid that serotonin is derived from, relative to a control group. The study showed that depression was induced within hours by lowering levels of tryptophan in those with risk factors for depression (Lam et al., 1996).

While serotonin's role in psychiatric disorders has been studied previously, its role in gastric disorders is lesser known. It is worth examining the role that serotonin plays in the gut to continue to understand the significance of the GBA and its implications for both psychiatric and gastric research and drug development.

Chapter 5: Serotonin, the Gut, and Inflammatory Bowel Disease

Serotonin plays a large role in gastrointestinal systems as 95% of serotonin is produced and stored in the enterochromaffin cells of the gastrointestinal tract. Serotonin is released from enterochromaffin cells in response to acetylcholine, sympathetic nerve stimulation, raised intraluminal pressure, and low pH (Banskota et al. 2019).

Serotonin activates neural reflexes and plays an integral role in intestinal secretion, sensation, and peristalsis. Serotonin's role is also relevant regarding nausea, vomiting, and general pain and discomfort in the gastrointestinal tract. Additionally, serotonin can act as a pro-inflammatory molecule and can regulate the immune cells in the gut. Some studies have shown that increased levels of serotonin in the gastrointestinal region can affect the level of severity of inflammation in IBD patients (Perez et al. 2022). Other studies found that IBD patients taking Selective Serotonin Reuptake Inhibitors (SSRI) suffered increased GI symptoms, possibly due to the increased availability of serotonin which can aid in the pathogenesis of. Research also showed that by blocking serotonin in the gut, symptoms, and severity of colitis were reduced colitis (Chojnacki et al. 2021). Additionally, serotonin was found to activate the gut immune cells to produce proinflammatory cytokine (Wan et al. 2020).

However, it's important to note that since anxiety and depression are comorbidities of IBD, SSRIs are often necessary to treat IBD patients. In general, people with chronic illnesses

suffer from anxiety and depression at higher rates than the public (Clarke & Currie, 2009). IBD patients have rates of lifelong anxiety and depression of 30%-50% and 20%-40%, respectively (Lewis et al., 2019; Brink et al. 2015). Recent studies have even shown that patients with gastrointestinal symptoms who were diagnosed with depression were at a higher risk for future IBD flares (Blackwell et al., 2020).

One theory for the high rates of depression and anxiety in IBD patients is the "inflammation-depression hypothesis" (Brink et al. 2015). This is a relatively new theory explaining depression through the lens of inflammation in the body. While attempts to understand the relationship between inflammation and depression have been fruitful, the specific mechanisms remain a mystery.

Generally, the "monoamine-depletion hypothesis" was the historic theory of depression's pathophysiology (Roohi et al. 2021). However, this theory seemed incomplete to many researchers. To further explore the causes of MDD, researchers began to explore the relationship between the peripheral immune system and MDD. Roohi et al. (2021) sought out to study this by establishing an immune cell profile of patients to study immune activation during MDD. They found that there seems to be associations between interleukin 6 (IL-6) activity, acute phase proteins, and "hyperactivity of the hypothalamic-pituitary-adrenal…axis" (Roohi et al. 2021). Many patients with Major Depressive Disorder (MDD) are also found to have elevated levels of inflammatory cytokines, such as IL-6. All of this suggests a more comprehensive and systemic forces at play in the pathogenesis of depression (Roohi et al. 2021).

Inflammation generally works in the body through the modulation of immune response genes. These include interleukin (IL)-1B, IL-6, and tumor necrosis factor (TNF) (Ott et al. 2007). All these immune response genes are responsible for promoting the secretion of proinflammatory

cytokines that result in system-wide inflammation (Darif et al. 2021). When the brain detects possible threats, inflammation in the body increases. Imminent stress can activate the "conserved transcriptional response to adversity" (CTRA) (Roohi et al. 2021) in response to a threat or infection. However, this response can also occur when true danger is absent. Normally, the CTRA response is "downregulated by the HPA axis" (Roohi et al. 2021) by cortisol. However, when there are long-term stressors or threats, resistance to glucocorticoids can develop. This resistance can lead to high levels of inflammation, raising one's risk of developing an inflammatory illness, like MDD and IBD (Roohi et al. 2021; Ott et al. 2000; Darif et al. 2021).

About one-third of IBD patients have been prescribed antidepressants for anxiety and depression. The types of medications that are often prescribed are serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and serotonin and norepinephrine inhibitors (SNRIs) which have known gastrointestinal effects (Byrne et al., 2017).

Researchers found that patients with preexisting depression were more likely to be diagnosed with IBD and antidepressant medication was found to protect against IBD (Frolkis et al., 2019). Researchers Kristensen et al., (2019) found that SSRIs have anti-inflammatory properties that can help treat IBD patients. These researchers conducted a study with IBD patients in Denmark and found that SSRIs were useful in treating IBD patients, especially those who had never taken SSRIs before, warranting further basis for exploring SSRIs in addition to conventional IBD treatment (Kristensen et al., 2019). This is especially important as recent studies have found that symptoms of depression and anxiety can trigger disease flare in IBD patients (Porcelli et al., 1996).

However, later research found that there could be a bidirectional relationship between mental health disorders and IBD flares due to the "brain-gut relationship" and found that relieving symptoms of depression and anxiety improved gut health (Gracie et al., 2018).

Gracie et al. (2018) demonstrated that IBD patients given SSRIs had a much lower disease flare rate than those who didn't take the medication (Gracie et al. 2018). However, those who hadn't taken the medication before the disease onset saw greater benefits than those who used the medications in the past (Gracie et al. 2018). Researchers hypothesized that perhaps, people who took SSRIs before IBD onset already received the anti-inflammatory benefits of the drug. Additionally, they hypothesized that patients who previously took SSRIs before disease onset have an increased risk for mental health challenges during disease onset, due to the stress of illness, leading to disease flare (Gracie et al. 2018).

Researchers haven't been able to distinguish whether the usage of SSRIs benefits IBD patients due to the improvement in mental health, which greatly affects gastrointestinal health, or the anti-inflammatory properties of the medication.

However, since IBD has no known cure, utilizing any treatments that improve the quality of life of IBD patients is vital. Since overall and most recently, SSRIs are helpful in conjunction with the traditional treatment of IBD, there is a need for further exploration to better understand the "brain-gut axis". Also, since the efficacy and positive effects of increased levels of serotonin due to SSRIs are debated, further study would be beneficial.

Chapter 6: Psychological Tools and Interventions for IBD and Depression/Anxiety

In addition to medication, there are other tools available to manage both IBD symptoms and anxiety/depression. One such tool is cognitive behavioral therapy (CBT). CBT is a type of

psychological treatment that seems to aid in the treatment of many psychiatric disorders. has been demonstrated to be effective for a range of problems including depression, anxiety disorders….and severe mental illness" (Oar et al. 2017).

There are a few principles for CBT practice. The first principle is to teach the patient that many psychological problems are partly, if not fully, based on unconstructive ways of thinking. The second principle is that psychological problems are also based on unhelpful thoughts and behaviors. Finally, CBT states that those suffering from psychological problems can learn coping skills to better navigate their mental health concerns and live a better life. At its core, CBT is a scientifically based means of attempting to change someone's thinking and behavioral patterns (Oar et al. 2017).

To change behavioral patterns, a therapist may encourage a client to actively face fears, engage in role-play to prepare for feared scenarios, and teach calming techniques to mitigate and manage mental health symptoms. Ultimately, the emphasis is on giving the individual tools and confidence to "graduate" from therapy and apply these skills for the rest of their lives. It emphasizes dealing with the present instead of fixating on the past, to teach one to move forward and cope with life's challenges.

There is mixed research on the application and outcomes of CBT's management of IBD outcomes. It is proven to be effective in alleviating symptoms of anxiety and depression with or without medication. However, it is unclear whether CBT can improve IBD disease outcomes and alleviate mental health symptoms specifically in IBD patients.

In a study by Mikocka-Walus et al. (2017) the effectiveness of CBT on physical outcomes in IBD and the long-term effectiveness of CBT was evaluated. After a randomized

controlled trial observing IBD patients undergoing CBT, the study found that CBT didn't greatly influence IBD activity or mental health status.

There are also studies evaluating the effectiveness of disease-specific cognitive-behavioral therapy. In a 2015 study by Brink et al., (2015) researchers assessed if treating depression can decrease gastrointestinal inflammation and improve IBD outcomes. The researchers conducted a randomized controlled trial to test how effective IBD-specific CBT is to reduce depression, anxiety, and improving disease outcomes and courses in adolescents with IBD. The researchers found that there was a "reduction in depressive and/or anxiety symptoms after 3 months and sustained remission for 12 months" (Brink et al. 2015). The researchers also found that the subject's quality of life improved along with their "psychosocial functioning" (Brink et al. 2015). Inflammatory cytokines in peripheral blood molecular cells were also assessed and were lowered than previously measured. Overall, IBD-specific CBT proved to be helpful for patients and seemed to overall improve their quality of life.

Another possible intervention is medical hypnotherapy. Medical hypnotherapy is when a provider guides the patient to a state of concentration and focus. This can help relax the patient and provide relief from both psychological and physical pain (Hauser et al. 2016).

Gut-directed hypnosis (GDH) is a specific form of medical hypnotherapy that was developed to reduce gastrointestinal (GI) distress in patients with IBS and IBD. This form of therapy is thought to modulate the brain-gut axis to improve both GI symptoms and psychosocial functioning. In a 2020 study by Pemberton et al., researchers conducted a qualitative study evaluating six practitioners trained in GDH. The idea is that reducing psychosocial symptoms can work within the brain-gut axis, thereby reducing overall inflammation in both the brain and body.

According to this study, GDH seems to impact GI functioning, reduce anxiety and depression, and improve cognitive functioning overall positively. Clinical trials have also shown that three months of GDH improved symptoms in GI patients (Pemberton et al. 2020). Other literature reviews have also found positive and significant results of GDH on GI patients. The specific mechanism remains unclear; however, it is likely related to the GBA and stress.

While the research on CBT and GDH needs further study, overall, it has shown to be a harmless and often helpful means of alleviating IBD and mental health symptoms.

Chapter 7: Dietary Tools and Interventions for IBD and Depression/Anxiety

The gut microbiome can also be manipulated to reduce symptoms of IBD and anxiety/depression. In a 2022 study by Olendzi et al., the role of dietary treatment for IBD was evaluated. According to the researchers, diet is a "modifiable, noninvasive, inexpensive behavior that is crucial in shaping the intestinal microbiome" (Olendzi et al. 2022).

This makes diet manipulation an attractive and vital tool in the treatment of IBD. Through an assessment of stool and blood samples as well as a dietary intake assessment, the efficacy of the IBD-Anti-Inflammatory Diet (IBD-AID) was analyzed. In addition, patients consumed prebiotics, probiotics, and foods associated with Clostridia and Bacteroides which are in low levels in people with IBD. These bacteria are particularly important due to their role in maintaining "gut homeostasis" by producing short-chain fatty acids (SCFAs) (Olendzi et al. 2022).

The study also reviewed some popular diets for the treatment of IBD. Trials have evaluated the efficacy of the Specific Carbohydrate Diet (SCD), the modified SCD with oats (mSCD), the Crohn's disease exclusion diet with partial enteral nutrition (CDED+PEN), and the

exclusive enteral nutrition (EEN) diet in pediatric patients. It was found that with SCD, mSCD, and a whole foods diet 100% of pediatric IBD patients were in remission within 12 weeks (Levine et al. 2019; Suskind et al. 2020). A study comparing CDED+PEN and EEN found that 63% and 67% of patients achieved remission after 3 and 6 weeks of treatment, respectively (Sigall et al. 2021). Overall, these diets were found to be high in Clostrida, like Faecalibacterium prausnitzii, Roseburia hominis, and Eubacterium eligens (Sigall et al. 2021; Suskind et al. 2020; Levine et al. 2019).

In adult patients, the SCD and Mediterranean diet has also been found to produce remission (Lewis et al. 2021). Studies found that after 6 weeks on either diet 50% of patients were in symptomatic remission or had a ≥30% reduction in fecal calprotectin levels.

The researchers in Olendzi et al. (2022) created the IBD-AID diet to improve the gut microbiome through the consumption of foods high in prebiotics and probiotics and avoid foods that trigger "intestinal symptoms and dysbiosis" (Olendzi et al. 2022). The researchers found that adult IBD patients on this diet had fewer symptoms and a reduced need for medication after 4 weeks on the IBD-AID diet.

In the same study it was also found that microbiotic interventions promoted the “1) biosynthesis of several key amino acids (i.e., histidine, lysine, threonine, methionine, serine, glycine, isoleucine, and arginine); 2) degradation of mannan (a dietary fiber); and 3) β-oxidation for fatty acid degradation" (Olendzi et al. 2022). Overall, it seemed that the IBD-AID diet increased the availability of SCFAs. The results showed that an increased level of consumption of prebiotics, probiotics, and other beneficial foods improves Clostridia and Bacteroides levels.

Additionally, as predicted, certain foods correlated with either lowered or raised levels of cytokines. Higher consumption of whole foods "negatively correlates with pro-inflammatory

cytokines" (Olendzi et al. 2022). Outside of the study, "high consumption of foods discouraged on the IBD-AID…relates to higher levels of pro-inflammatory cytokines" (Olendzi et al. 2022). The study concluded that a diet rich in fiber, probiotics, and other beneficial food like lean animal protein and omega-3 fatty acids can help with the production of anti-inflammatory bacteria like Clostridia and Bacteroides (Olendzi et al. 2022).

Similarly, researchers have evaluated the effect of diet on depression. A 2017 study by Parletta et al. evaluated the effects of diet on mental health symptoms. Researchers found that a Mediterranean diet high in omega-3 and low in omega-6 improved mental health overall and noted the use of supplemental fish oil to provide an extra boost of omega-3s in mentally ill patients (Parletta et al. 2017).

Since depression has only recently been associated with chronic inflammation, researchers Belliveau et al. (2022) set out to evaluate the role of one's diet in promoting inflammation in the body. Foods such as sugar, refined flour, saturated fats, and red and processed meat can contribute to inflammation. Along with promoting health conditions like cardiovascular disease, diabetes, cancers, and neurocognitive disorders, this diet is now linked with an increased chance of depression (Belliveau et al. 2022). Since the brain's neurotransmitters need proper amino acids, vitamins, and minerals to function, deficits in key nutrients can increase one's risk of developing depression.

The Empirical Dietary Inflammatory Index (EDII) "focuses on weekly consumption of sixteen net pro-or anti-inflammatory food groups" (Belliveau et al. 2022). Using the EDII, researchers attempt to understand the relationship between symptoms of depression and high EDII scores. It has been demonstrated that a pro-inflammatory, high EDII score was associated with increased symptoms of depression. This supports the use of diet as a method of treating all

inflammatory conditions, along with providing evidence of depression's inflammatory nature (Belliveau et al. 2022).

It is clear from existing literature that an anti-inflammatory diet plays a massive role in modulating symptoms of both IBD and depression/anxiety. Overall, it seems that the Mediterranean Diet seems to be the most highly regarded anti-inflammatory diet. A manipulation of the gut microbiome through dietary means could prove quite life changing as another tool to manage symptoms of both IBD and depression.

Chapter 8: Lifestyle Tools and Interventions for IBD and Depression/Anxiety

Since chronic stress is proven to be a cause of inflammation in the body, thereby contributing to both IBD and depression/anxiety, researchers have evaluated lifestyle changes to lower stress in a patient's life.

A 2019 study by Shuch & Stubbs (2019) aimed to evaluate the role of exercise in both the treatment and prevention of depression. In the literature, it is seen that exercise can both reduce symptoms and protect against depression. However, noting the heterogeneity of the effects of exercise, identifying which people are at risk to benefit less from exercise in the treatment and prevention of depression will be important in guiding future research and developing comprehensive treatment plans. Several studies have shown that people with greater levels of physical activity have decreased symptoms of depression. This is due to the endorphins released during exercise binding to the brain's opiate centers and triggering the release of dopamine (Mikkelsen et al. 2017). These findings are consistent across countries and cultures.

A study by Shuch & Stubbs (2019) study cited evidence from the Brazilian National Healthy Survey, which showed an association between a lack of exercise and depression in young males. Similarly, the study cited data from a study conducted on older Japanese adults, and in the United States. The researchers conducted a meta-analysis of all available data on exercise and depression, and it seems that people with depression "have about a 50% higher chance of not meeting the 150 minutes of moderate to vigorous PA as recommended by the general public health guidelines" (Shuch & Stubbs 2019).

Previous literature reviews have named some factors that can predict whether symptoms of depression will respond positively to exercise. Higher levels of brain-derived neurotrophic factor (BDNF), IL-1β, and TNF-α are associated with a greater response to exercise (Malczynska-Sims et al. 2020).

Interestingly, elevated levels of TNF-α and IL-6 are also associated with a pro-inflammatory state as seen in leaky gut syndrome. This could provide even stronger evidence for the significance of exercise in patients with both gastrointestinal inflammation and depression/anxiety. There are also clinical psychosocial predictors as to whether someone will respond positively to exercise. Overall better functioning and social support seem to indicate that someone will respond more greatly to exercise benefits in preventing and treating depression (Craft & Perna 2004).

Regarding inflammation, exercise can promote an increase in "anti-inflammatory and antioxidant enzymes" (Shuch & Stubbs 2019). These enzymes can combat the elevated inflammatory markers like IL-6 and IL-1β present in both depressed people and people with IBD. Exercise can also promote neuroplasticity and increase hippocampal volume, increasing brain activity and reducing symptoms (Shuch & Stubbs 2019).

Researchers have also evaluated the role of exercise in patients with IBD. In a 2017 study by Engels et al., researchers hypothesized that "moderate-intensity exercise exerts an anti-inflammatory effect by both decreasing visceral fat and… [the release of] pro-inflammatory cytokines and releasing myokines…[like] IL-6" (Engles et al. 2017). The IL-6 that is released during exercise can also promote the release of "glucagon-like peptides." These peptides are associated with the repair of damage in the mucosa of the intestine. Exercise has also been found to decrease the expression of pro-inflammatory cytokines such as like TNF-α and IL-1β and increase the expression of anti-inflammatory cytokines including IL-10 (Engles et al. 2017).

From research on the role of exercise in reducing inflammation for both people with IBD and depression, the similar anti-inflammatory mechanisms through which exercise provides benefits further support the innumerable connections between the brain and the gut. For both conditions, especially in those who suffer from both, it is vital to prevent and treat symptoms to obtain regular exercise, in any form attainable for each patient.

Another lifestyle change studied for its effects on lowering inflammation is integrating meditative practices and mindfulness. In a 2016 article by Black & Slavich, researchers assessed the effects of meditation and mindfulness on the immune system. Researchers defined this practice as "the awareness that emerges through paying attention on purpose, in the present moment, and nonjudgmentally to the unfolding of experience moment by moment" (Black & Slavich 2016). Their review and analysis of currently available data on the effects of mindfulness and meditation on certain biological markers found effects in four areas. First, it seems there is a reduction in the actions of the "cellular transcription factor NF-κB", a protein complex that is implicated in promoting inflammation (Black & Slavich 2016). There also seemed to be reductions in C-reactive protein levels, another inflammation marker. While from an

inflammatory perspective there is still much evidence needed to support meditation's role in acting as an anti-inflammation measure, there is great promise for future research.

The reduction of stress promoted by meditation is extremely beneficial for lowering inflammation in the body and can help mitigate symptoms of both IBD and depression. Through a meta-analysis of the neurobiological effects of meditation, Pascoe et al. (2017) found that meditation reduced many biological markers of stress including cortisol, C-reactive protein, blood pressure, heart rate, triglycerides, and inflammatory cytokines (Pascoe et al. 2017). There is a substantial basis for patients with IBD, depression, or both to integrate meditative practice to reduce psychological stress and subsequent biological inflammatory markers of stress.

Exercise seems to be another means of reducing inflammation in the body with minimal risks and side effects. Beyond the obvious aesthetic and health benefits of exercise, research seems to support its role in mitigating symptoms of depression and IBD through the different mechanisms noted above.

Chapter 9: Alternative Therapies—Ketamine

As the scientific community continues to look for alternative means of lowering inflammation in the body to treat an array of illnesses, especially IBD and depression, some researchers have begun to explore the use of alternative therapies.

Ketamine, a "noncompetitive antagonist of N-methyl-d-aspartate" (NMDA) has both anesthetic and rapid antidepressant properties (Yu et al. 2016). Through activation of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors and molecular signaling of mTOR (the mammalian target of rapamycin), enhancing hippocampal brain-derived neurotrophic factor (BDNF) and increased synaptogenesis, Ketamine aids in treatment-resistant depression

(Getachew et al. 2018). Ketamine therapy for treatment-resistant depression and the treatment of IBD is being explored. While traditional antidepressants act via the monoaminergic systems (Trujilo et al. 2011), ketamine elicits its effects by interacting with glutamate receptors. It has rapid long-lasting antidepressant effects, which can be lifesaving for people suffering from treatment resistant chronic Major Depressive Disorder.

Researchers Sukhram et al. (2022) set out to understand the anti-depressant effects of ketamine from an inflammation perspective. Previous research has identified ketamine's anti-inflammatory effect through the modulation of certain proinflammatory cytokines. Prior clinical studies have also indicated ketamine's antidepressant effects on the regulation of the peripheral and central immune systems. Ketamine is thought to lower pro-inflammatory cytokine levels and is thought to be associated with the ability to suppress proinflammatory molecules like IL-1β, IL-6, and TNF-α. New data even suggests that ketamine's antidepressant effects work by blocking IL-6, a pro-inflammatory molecule (Sukrham et al. 2022). It's important to note that this is a relatively new area of research and discovery, and more advancements need to be made to confirm the relationship between cytokines and ketamine's antidepressant mechanisms. There is great potential for further research to be done.

In the area of ketamine and the gut, researchers Getachew et al. (2018) evaluated ketamine interactions with the gut microbiota of rats to understand ketamine's antidepressant and anti-inflammatory properties. Getachew et al. found that ketamine magnified the bacteria Lactobacillus, Turibacter, and Sacrina. Lactobacillus was amplified by 3.3-fold, Turibacter by 26-fold, and Sacrina by 42-fold. The researchers noted how low levels of certain bacteria, specifically Lactobacillus and Turicibacter are often associated with depressive behaviors in

animals. Therefore, the researchers have evidence to support the potential role of the gut microbiota in depression and ketamine's antidepressant effects through the gut.

High levels of the bacteria Ruminococcus are associated with intense symptoms of IBS, and some types of Mucispirillum bacteria have been associated with inflammation in the intestines. There is also evidence for the anti-inflammatory role of Sarcina. In this Getachew et al. (2018) rodent study, researchers found that some of the antidepressant and anti-inflammatory effects after a 7-day treatment of ketamine are mediated through ketamine's interaction with certain bacteria in the rodent gut (Getachew et al. 2018).

It seems from all the available and current research that dysbiosis, meaning an imbalance in the gut microbiota, can happen during depression and a state of chronic stress because of an alteration of brain signaling to the gut. Significantly, some antidepressants have antimicrobial properties (Getachew et al. 2018), and germ-free animals have been shown to exhibit depressed behavior. The researchers hypothesized that ketamine would boost microbiota that are found to elevate mood and suppress microbiota that are found to be pro-inflammatory (Getachew et al. 2018).

The data in the Getachew study showed very significant effects of "chronic low dose ketamine on gut microbial ecology, ranging from 2 to 42-fold changes in specific genera" (Getachew et al. 2018). Overall, anti-inflammatory bacteria were amplified whereas pro-inflammatory bacteria were reduced, suggesting a strong foundation for ketamine's anti-inflammatory effects.

Earlier research from 2011 by Loix et al. provided evidence that ketamine is "an anti-proinflammatory drug" (Loix et al. 2011). Meaning, ketamine "avoids the extension and exacerbation of inflammation without blunting the local processes" (Loix et al. 2011). This is

especially significant given that many current anti-inflammatory drugs suppress the immune system and make the patient vulnerable to a whole host of viruses and bacteria. Loix et al. (2011) note that "Ketamine has immunomodulatory properties without being immunosuppressive."

However, ketamine therapy does carry some risk, especially since it's only recently been approved as a treatment for depression. The main side effects are dissociation, intoxication, sedation, high blood pressure, dizziness, headache, blurred vision, anxiety, nausea, and vomiting. It also isn't used on patients with a history of psychosis, substance use disorder, teenagers, pregnant women, or older adults with dementia (Jelen & Stone 2021).

However, for any inflammatory condition, especially patients with IBD and comorbid depression, further research on ketamine therapy holds a lot of promise for its anti-inflammatory effects and potential to greatly relieve the suffering of millions of people.

Chapter 10: Conclusion and Future Research Directions

There is a clear, significant, and symbiotic relationship between the brain and the gut. Through the lens of the brain-gut axis and inflammation, there is much evidence to support the use of dual-purpose therapies to relieve the suffering of IBD patients, depressed patients, and IBD patients with depression.

There are many tools and resources available to navigate inflammation in the body, and it is quite clear that inflammation is a fully systemic disorder that affects a whole host of biological and psychological functioning.

Future research should focus on a greater understanding of the mechanisms behind the gut-brain axis and explore that connection to develop advanced drugs that comprehensively treat each patient's specific symptoms and needs. Ketamine is particularly interesting due to its

immunomodulatory properties without immunosuppressant side effects. Because its clinical use is relatively new, this is a significant area for researchers to explore as a means of treating systemic inflammation. The ability to treat IBD without suppressing the immune system would be lifechanging for many IBD patients who suffer remain at risk for many illnesses due to their limited immune system.

The body is one system, with pathways and interactions that seem increasingly intricate and interdependent as scientific research advances. Our increasing awareness and understanding of these interactions will help create treatment plans and biopharmaceuticals that comprehensively treat each patient's individual illness and symptoms.

Additionally, the low-risk methods for controlling symptoms of IBD and depression like diet, exercise, and therapy should not be undervalued. There is significant evidence that these methods can substantially help patients suffering from inflammation-related illnesses, whether that be from the brain, the gut, or both.

This is an exciting and emerging area of research with so much potential to catalyze the scientific community's understanding of the large role of inflammation plays in our health. Through an understanding of the unique connection between the gut and the brain, possibilities are wide open for creating treatment plans and medications that are safe, effective, and most importantly: have long-lasting, if not permanent, results.

Works Cited

Agirman, G., Yu, K. B., & Hsiao, E. Y. (2021). Signaling inflammation across the gut-brain axis. *Science*, *374*(6571), 1087–1092. https://doi.org/10.1126/science.abi6087

Ananthakrishnan, A. N. (2015). Epidemiology and risk factors for IBD. *Nature Reviews Gastroenterology & Hepatology*, *12*(4), 205–217. https://doi.org/10.1038/nrgastro.2015.34

Asadi, A., Shadab Mehr, N., Mohamadi, M. H., Shokri, F., Heidary, M., Sadeghifard, N., & Khoshnood, S. (2022). Obesity and gut–microbiota–brain axis: A narrative review. *Journal of Clinical Laboratory Analysis*, *36*(5). https://doi.org/10.1002/jcla.24420

Averina, O. V., Zorkina, Y. A., Yunes, R. A., Kovtun, A. S., Ushakova, V. M., Morozova, A. Y., Kostyuk, G. P., Danilenko, V. N., & Chekhonin, V. P. (2020). Bacterial metabolites of human gut microbiota correlating with depression. *International Journal of Molecular Sciences*, *21*(23), 9234. https://doi.org/10.3390/ijms21239234

Banskota, S., Ghia, J.-E., & Khan, W. I. (2019). Serotonin in the gut: Blessing or a curse. *Biochimie*, *161*, 56–64. https://doi.org/10.1016/j.biochi.2018.06.008

Belliveau, R., Horton, S., Hereford, C., Ridpath, L., Foster, R., & Boothe, E. (2022). Pro-inflammatory diet and depressive symptoms in the healthcare setting. *BMC Psychiatry*, *22*(1). https://doi.org/10.1186/s12888-022-03771-z

Black, D. S., & Slavich, G. M. (2016). Mindfulness meditation and the immune system: A systematic review of randomized controlled trials. *Annals of the New York Academy of Sciences*, *1373*(1), 13–24. https://doi.org/10.1111/nyas.12998

Blackwell, J., Saxena, S., Petersen, I., Hotopf, M., Creese, H., Bottle, A., Alexakis, C., & Pollok, R. C. (2020). Depression in individuals who subsequently develop inflammatory bowel

disease: A population-based nested case–Control Study. *Gut*, *70*(9), 1642–1648. https://doi.org/10.1136/gutjnl-2020-322308

Brink, G. van den, Stapersma, L., Marroun, H. E., Henrichs, J., Szigethy, E. M., Utens, E. M. W. J., & Escher, J. C. (2016, March 1). *Effectiveness of disease-specific cognitive–behavioural therapy on depression, anxiety, quality of life and the clinical course of disease in adolescents with inflammatory bowel disease: Study protocol of a multicentre randomised controlled trial (happy-IBD)*. BMJ Open Gastroenterology. Retrieved December 8, 2022, from https://bmjopengastro.bmj.com/content/3/1/e000071

Byrne, G., Rosenfeld, G., Leung, Y., Qian, H., Raudzus, J., Nunez, C., & Bressler, B. (2017). Prevalence of anxiety and depression in patients with inflammatory bowel disease. *Canadian Journal of Gastroenterology and Hepatology*, *2017*, 1–6. https://doi.org/10.1155/2017/6496727

Catani, M. (2019). The anatomy of the human frontal lobe. *The Frontal Lobes*, 95–122. https://doi.org/10.1016/b978-0-12-804281-6.00006-9

Chojnacki, C., Popławski, T., Gasiorowska, A., Chojnacki, J., & Blasiak, J. (2021). Serotonin in the pathogenesis of lymphocytic colitis. *Journal of Clinical Medicine*, *10*(2), 285. https://doi.org/10.3390/jcm10020285

Clarke, D. M., & Currie, K. C. (2009). Depression, anxiety and their relationship with chronic diseases: A review of the epidemiology, risk and treatment evidence. *Medical Journal of Australia*, *190*(S7). https://doi.org/10.5694/j.1326-5377.2009.tb02471.x

Costa, M. (2000). Anatomy and physiology of the enteric nervous system. *Gut*, *47*(90004), 15iv–19. https://doi.org/10.1136/gut.47.suppl_4.iv15

Cowen, P. J., & Browning, M. (2015). What has serotonin to do with depression? *World Psychiatry*, *14*(2), 158–160. https://doi.org/10.1002/wps.20229

Craft, L. L., & Perna, F. M. (2004). The benefits of exercise for the clinically depressed. *The Primary Care Companion to The Journal of Clinical Psychiatry*, *06*(03), 104–111. https://doi.org/10.4088/pcc.v06n0301

Cresci, G. A., & Bawden, E. (2015). Gut microbiome. *Nutrition in Clinical Practice*, *30*(6), 734–746. https://doi.org/10.1177/0884533615609899

Darif, D., Hammi, I., Kihel, A., El Idrissi Saik, I., Guessous, F., & Akarid, K. (2021). The pro-inflammatory cytokines in COVID-19 pathogenesis: What goes wrong? *Microbial Pathogenesis*, *153*, 104799. https://doi.org/10.1016/j.micpath.2021.104799

Dicks, L. M., Hurn, D., & Hermanus, D. (2021). Gut bacteria and neuropsychiatric disorders. *Microorganisms*, *9*(12), 2583. https://doi.org/10.3390/microorganisms9122583

Dieterich, M., & Brandt, T. (2018). The parietal lobe and the vestibular system. *Handbook of Clinical Neurology*, 119–140. https://doi.org/10.1016/b978-0-444-63622-5.00006-1

Foster, J. A., Baker, G. B., & Dursun, S. M. (2021). The relationship between the gut microbiome-immune system-brain axis and major depressive disorder. *Frontiers in Neurology*, *12*. https://doi.org/10.3389/fneur.2021.721126

Friederici, A. D. (2011). The brain basis of language processing: From structure to function. *Physiological Reviews*, *91*(4), 1357–1392. https://doi.org/10.1152/physrev.00006.2011

Gao, K., Mu, C.-long, Farzi, A., & Zhu, W.-yun. (2019). Tryptophan metabolism: A link between the gut microbiota and brain. *Advances in Nutrition*, *11*(3), 709–723. https://doi.org/10.1093/advances/nmz127

Getachew, B., Aubee, J. I., Schottenfeld, R. S., Csoka, A. B., Thompson, K. M., & Tizabi, Y. (2018). Ketamine interactions with gut-microbiota in rats: Relevance to its antidepressant and anti-inflammatory properties. *BMC Microbiology*, *18*(1). https://doi.org/10.1186/s12866-018-1373-7

Gracie, D. J., Guthrie, E. A., Hamlin, P. J., & Ford, A. C. (2018). Bi-directionality of brain–gut interactions in patients with inflammatory bowel disease. *Gastroenterology*, *154*(6). https://doi.org/10.1053/j.gastro.2018.01.027

Heiss, C. N., & Olofsson, L. E. (2019). The role of the gut microbiota in development, function and disorders of the central nervous system and the Enteric Nervous System. *Journal of Neuroendocrinology*, *31*(5). https://doi.org/10.1111/jne.12684

Hornung, J.-P. (2010). The neuronatomy of the serotonergic system. *Handbook of Behavioral Neuroscience*, 51–64. https://doi.org/10.1016/s1569-7339(10)70071-0

Hyun, J. G., & Mayer, L. (2006). Mechanisms underlying inflammatory bowel disease. *Drug Discovery Today: Disease Mechanisms*, *3*(4), 457–462. https://doi.org/10.1016/j.ddmec.2006.11.010

Häuser, W., Hagl, M., Schmierer, A., & Hansen, E. (2016). The efficacy, safety and applications of Medical Hypnosis: A systematic review of Meta-analyses. *Deutsches Ärzteblatt International*. https://doi.org/10.3238/arztebl.2016.0289

Jelen, L. A., & Stone, J. M. (2021). Ketamine for depression. *International Review of Psychiatry*, *33*(3), 207–228. https://doi.org/10.1080/09540261.2020.1854194

Jonnakuty, C., & Gragnoli, C. (2008). What do we know about serotonin? *Journal of Cellular Physiology*, *217*(2), 301–306. https://doi.org/10.1002/jcp.21533

Kast, R. E. (2003). Anti- and pro-inflammatory considerations in antidepressant use during medical illness: Bupropion lowers and mirtazapine increases circulating tumor necrosis factor-alpha levels. *General Hospital Psychiatry*, *25*(6), 495–496. https://doi.org/10.1016/s0163-8343(03)00093-8

Kristensen, M. S., Kjærulff, T. M., Ersbøll, A. K., Green, A., Hallas, J., & Thygesen, L. C. (2018). The influence of antidepressants on the disease course among patients with crohn's disease and ulcerative colitis—a Danish nationwide register–based Cohort Study. *Inflammatory Bowel Diseases*, *25*(5), 886–893. https://doi.org/10.1093/ibd/izy367

Lam, R. W. (1996). Effects of rapid tryptophan depletion in patients with seasonal affective disorder in remission after light therapy. *Archives of General Psychiatry*, *53*(1), 41. https://doi.org/10.1001/archpsyc.1996.01830010043007

Levine, A., Wine, E., Assa, A., Sigall Boneh, R., Shaoul, R., Kori, M., Cohen, S., Peleg, S., Shamaly, H., On, A., Millman, P., Abramas, L., Ziv-Baran, T., Grant, S., Abitbol, G., Dunn, K. A., Bielawski, J. P., & Van Limbergen, J. (2019). Crohn's disease exclusion diet plus partial enteral nutrition induces sustained remission in a randomized controlled trial. *Gastroenterology*, *157*(2). https://doi.org/10.1053/j.gastro.2019.04.021

Lewis, J. D., Sandler, R. S., Brotherton, C., Brensinger, C., Li, H., Kappelman, M. D., Daniel, S. G., Bittinger, K., Albenberg, L., Valentine, J. F., Hanson, J. S., Suskind, D. L., Meyer, A., Compher, C. W., Bewtra, M., Saxena, A., Dobes, A., Cohen, B. L., Flynn, A. D., … Herfarth, H. (2021). A randomized trial comparing the specific carbohydrate diet to a Mediterranean diet in adults with crohn's disease. *Gastroenterology*, *161*(3). https://doi.org/10.1053/j.gastro.2021.05.047

Lewis, K., Marrie, R. A., Bernstein, C. N., Graff, L. A., Patten, S. B., Sareen, J., Fisk, J. D., Bolton, J. M., Marrie, R. A., Bolton, J. M., Sareen, J., Walker, J. R., Patten, S. B., Singer, A., Lix, L. M., Hitchon, C. A., El-Gabalawy, R., Katz, A., Fisk, J. D., … Marriott, J. (2019). The prevalence and risk factors of undiagnosed depression and anxiety disorders among patients with inflammatory bowel disease. *Inflammatory Bowel Diseases*, *25*(10), 1674–1680. https://doi.org/10.1093/ibd/izz045

Liu, Y., Lin, D., Wu, B., & Zhou, W. (2016). Ketamine abuse potential and use disorder. *Brain Research Bulletin*, *126*, 68–73. https://doi.org/10.1016/j.brainresbull.2016.05.016

Marek, S., & Dosenbach, N. U. F. (2019). Control networks of the frontal lobes. *The Frontal Lobes*, 333–347. https://doi.org/10.1016/b978-0-12-804281-6.00018-5

Małczyńska-Sims, P., Chalimoniuk, M., & Sułek, A. (2020). The effect of endurance training on brain-derived neurotrophic factor and inflammatory markers in healthy people and parkinson's disease. A narrative review. *Frontiers in Physiology*, *11*. https://doi.org/10.3389/fphys.2020.578981

MD;, E. M. C. R. K. L. (n.d.). *Exercise in patients with inflammatory bowel diseases: Current perspectives*. Clinical and experimental gastroenterology. Retrieved December 13, 2022, from https://pubmed.ncbi.nlm.nih.gov/29317842/

Mercado, N. M., Zhang, G., Ying, Z., & Gómez-Pinilla, F. (2022). Traumatic brain injury alters the gut-derived serotonergic system and associated peripheral organs. *Biochimica Et Biophysica Acta (BBA) - Molecular Basis of Disease*, *1868*(11), 166491. https://doi.org/10.1016/j.bbadis.2022.166491

Mikkelsen, K., Stojanovska, L., Polenakovic, M., Bosevski, M., & Apostolopoulos, V. (2017). Exercise and mental health. *Maturitas*, *106*, 48–56. https://doi.org/10.1016/j.maturitas.2017.09.003

Mikocka-Walus, A., Andrews, J. M., & Bampton, P. (2016). Cognitive behavioral therapy for IBD. *Inflammatory Bowel Diseases*, *22*(2). https://doi.org/10.1097/mib.0000000000000672

Mikocka-Walus, A., Bampton, P., Hetzel, D., Hughes, P., Esterman, A., & Andrews, J. M. (2016, July 18). *Cognitive-behavioural therapy for inflammatory bowel disease: 24-month data from a randomised controlled trial - International Journal of Behavioral Medicine*. SpringerLink. Retrieved December 8, 2022, from https://link.springer.com/article/10.1007/s12529-016-9580-9

Murphy, S. E., Capitão, L. P., Giles, S. L., Cowen, P. J., Stringaris, A., & Harmer, C. J. (2021). The knowns and unknowns of SSRI treatment in young people with depression and anxiety: Efficacy, predictors, and mechanisms of action. *The Lancet Psychiatry*, *8*(9), 824–835. https://doi.org/10.1016/s2215-0366(21)00154-1

Nezami, B. G., & Srinivasan, S. (2010). Enteric nervous system in the small intestine: Pathophysiology and clinical implications. *Current Gastroenterology Reports*, *12*(5), 358–365. https://doi.org/10.1007/s11894-010-0129-9

Oar, E. L., Johnco, C., & Ollendick, T. H. (2017). Cognitive behavioral therapy for anxiety and depression in children and adolescents. *Psychiatric Clinics of North America*, *40*(4), 661–674. https://doi.org/10.1016/j.psc.2017.08.002

Obrenovich, M. (2018). Leaky gut, leaky brain? *Microorganisms*, *6*(4), 107. https://doi.org/10.3390/microorganisms6040107

Olendzki, B., Bucci, V., Cawley, C., Maserati, R., McManus, M., Olednzki, E., Madziar, C., Chiang, D., Ward, D. V., Pellish, R., Foley, C., Bhattarai, S., McCormick, B. A., & Maldonado-Contreras, A. (2022). Dietary manipulation of the gut microbiome in inflammatory bowel disease patients: Pilot study. *Gut Microbes*, *14*(1). https://doi.org/10.1080/19490976.2022.2046244

Oostenbrug, L. E., Dullemen, H. M., Meerman, G. J., & Jansen, P. L. (2003). IBD and Genetics: New developments. *Scandinavian Journal of Gastroenterology*, *38*, 63–68. https://doi.org/10.1080/00855920310002717

Ott, L. W., Resing, K. A., Sizemore, A. W., Heyen, J. W., Cocklin, R. R., Pedrick, N. M., Woods, H. C., Chen, J. Y., Goebl, M. G., Witzmann, F. A., & Harrington, M. A. (2007). Tumor necrosis factor-α- and interleukin-1-induced cellular responses: coupling proteomic and genomic information. *Journal of Proteome Research*, *6*(6), 2176–2185. https://doi.org/10.1021/pr0606651

O'Mahony, S. M., Clarke, G., Borre, Y. E., Dinan, T. G., & Cryan, J. F. (2015). Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. *Behavioural Brain Research*, *277*, 32–48. https://doi.org/10.1016/j.bbr.2014.07.027

Parkin, J., & Cohen, B. (2001). An overview of the immune system. *The Lancet*, *357*(9270), 1777–1789. https://doi.org/10.1016/s0140-6736(00)04904-7

Parletta, N., Zarnowiecki, D., Cho, J., Wilson, A., Bogomolova, S., Villani, A., Itsiopoulos, C., Niyonsenga, T., Blunden, S., Meyer, B., Segal, L., Baune, B. T., & O'Dea, K. (2017). A Mediterranean-style dietary intervention supplemented with fish oil improves diet quality and mental health in people with depression: A randomized controlled trial

(HELFIMED). *Nutritional Neuroscience*, *22*(7), 474–487. https://doi.org/10.1080/1028415x.2017.1411320

Pascoe, M. C., Thompson, D. R., Jenkins, Z. M., & Ski, C. F. (2017). Mindfulness mediates the physiological markers of stress: Systematic Review and meta-analysis. *Journal of Psychiatric Research*, *95*, 156–178. https://doi.org/10.1016/j.jpsychires.2017.08.004

Pemberton, L., Kita, L., & Andrews, K. (2020). Practitioners' experiences of using gut directed hypnosis for irritable bowel syndrome: Perceived impact upon client wellbeing: A qualitative study. *Complementary Therapies in Medicine*, *55*, 102605. https://doi.org/10.1016/j.ctim.2020.102605

Perez, F., Kotecha, N., Lavoie, B., Mawe, G. M., & Patel, B. A. (2022). Monitoring gut epithelium serotonin and melatonin overflow provides spatial mapping of inflammation. *ChemBioChem*. https://doi.org/10.1002/cbic.202200334

Piovani, D., Danese, S., Peyrin-Biroulet, L., Nikolopoulos, G. K., Lytras, T., & Bonovas, S. (2019). Environmental risk factors for inflammatory bowel diseases: An umbrella review of Meta-analyses. *Gastroenterology*, *157*(3). https://doi.org/10.1053/j.gastro.2019.04.016

Pittayanon, R., Lau, J. T., Yuan, Y., Leontiadis, G. I., Tse, F., Surette, M., & Moayyedi, P. (2019). Gut microbiota in patients with irritable bowel syndrome—a systematic review. *Gastroenterology*, *157*(1), 97–108. https://doi.org/10.1053/j.gastro.2019.03.049

Porcell, P., Leoci, C., & Guerra, V. (1996). A prospective study of the relationship between disease activity and psychologic distress in patients with inflammatory bowel disease. *Scandinavian Journal of Gastroenterology*, *31*(8), 792–796. https://doi.org/10.3109/00365529609010354

Rao, M., & Gershon, M. D. (2016). The bowel and beyond: The enteric nervous system in neurological disorders. *Nature Reviews Gastroenterology & Hepatology*, *13*(9), 517–528. https://doi.org/10.1038/nrgastro.2016.107

Roohi, E., Jaafari, N., & Hashemian, F. (2021, February 16). *On inflammatory hypothesis of depression: What is the role of IL-6 in the middle of the chaos? - journal of Neuroinflammation*. BioMed Central. Retrieved December 12, 2022, from https://jneuroinflammation.biomedcentral.com/articles/10.1186/s12974-021-02100-7

S, L., M De, K., & P, H. (2011). The anti-inflammatory effects of ketamine: state of the art. *Cta Anaesthesiologica Belgica*, *1*(62), 47–58.

Schmidt, T. S. B., Raes, J., & Bork, P. (2018). The human gut microbiome: From Association to Modulation. *Cell*, *172*(6), 1198–1215. https://doi.org/10.1016/j.cell.2018.02.044

Schuch, F. B., & Stubbs, B. (2019). The role of exercise in preventing and treating depression. *Current Sports Medicine Reports*, *18*(8), 299–304. https://doi.org/10.1249/jsr.0000000000000620

Sukhram, S. D., Yilmaz, G., & Gu, J. (2022). Antidepressant effect of ketamine on inflammation-mediated cytokine dysregulation in adults with treatment-resistant depression: Rapid Systematic Review. *Oxidative Medicine and Cellular Longevity*, *2022*, 1–13. https://doi.org/10.1155/2022/1061274

Suskind, D. L., Lee, D., Kim, Y.-M., Wahbeh, G., Singh, N., Braly, K., Nuding, M., Nicora, C. D., Purvine, S. O., Lipton, M. S., Jansson, J. K., & Nelson, W. C. (2020). The specific carbohydrate diet and diet modification as induction therapy for pediatric crohn's disease: A randomized diet controlled trial. *Nutrients*, *12*(12), 3749. https://doi.org/10.3390/nu12123749

Trujillo, K. A., Smith, M. L., Sullivan, B., Heller, C. Y., Garcia, C., & Bates, M. (2011). The neurobehavioral pharmacology of ketamine: Implications for drug abuse, addiction, and Psychiatric Disorders. *ILAR Journal*, *52*(3), 366–378. https://doi.org/10.1093/ilar.52.3.366

van den Brink, G., Stapersma, L., El Marroun, H., Henrichs, J., Szigethy, E. M., Utens, E. M. W. J., & Escher, J. C. (2016). Effectiveness of disease-specific cognitive–behavioural therapy on depression, anxiety, quality of life and the clinical course of disease in adolescents with inflammatory bowel disease: Study protocol of a multicentre randomised controlled trial (happy-IBD). *BMJ Open Gastroenterology*, *3*(1). https://doi.org/10.1136/bmjgast-2015-000071

Wan, M., Ding, L., Wang, D., Han, J., & Gao, P. (2020). Serotonin: A potent immune cell modulator in autoimmune diseases. *Frontiers in Immunology*, *11*. https://doi.org/10.3389/fimmu.2020.00186

WI;, K. (2013, April). *The role of 5-HT dysregulation in inflammatory bowel disease*. Gastroenterology & hepatology. Retrieved December 8, 2022, from https://pubmed.ncbi.nlm.nih.gov/24711774/

Windsor, J. W., & Kaplan, G. G. (2019). Evolving Epidemiology of IBD. *Current Gastroenterology Reports*, *21*(8). https://doi.org/10.1007/s11894-019-0705-6

Yu, Y. R., & Rodriguez, J. R. (2017). Clinical presentation of Crohn's, ulcerative colitis, and indeterminate colitis: Symptoms, extraintestinal manifestations, and disease phenotypes. *Seminars in Pediatric Surgery*, *26*(6), 349–355. https://doi.org/10.1053/j.sempedsurg.2017.10.003

Yunes, R. A., Poluektova, E. U., Dyachkova, M. S., Klimina, K. M., Kovtun, A. S., Averina, O. V., Orlova, V. S., & Danilenko, V. N. (2016). GABA production and structure of gadB / GADC genes in Lactobacillus and Bifidobacterium strains from human microbiota. *Anaerobe*, *42*, 197–204. https://doi.org/10.1016/j.anaerobe.2016.10.011

Zhang, Y.-Z. (2014). Inflammatory bowel disease: Pathogenesis. *World Journal of Gastroenterology*, *20*(1), 91. https://doi.org/10.3748/wjg.v20.i1.91