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The Significance of the Impact of Stress's Role in Inflammatory Bowel Disease

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ABSTRACT

Diseases of the gastrointestinal tract have somewhat recently become more common among society. Of these diseases, one example acquiring a lot of attention is inflammatory bowel disease, also known as IBD. Though literature on the disease's etiology and pathogenesis is available, the influence of environmental factors remains largely inconclusive. An example of an ambiguous environmental factor is stress. Studies on the role of stress in IBD have produced conflicting results. While there is a potential relationship between stress and inflammatory bowel disease activity, its significance has not been settled across research. This paper examines the relationship between IBD and stress in scientific literature, and in the context of patient anecdotes. Stress is also examined as a potential target of treatment through the implementation of mindfulness-based interventions. Other factors with inconclusive relationships to IBD are noted as potential influences on disease activity that warrant attention, due to their potential to be used as targets of treatment to reduce IBD symptoms. The purpose of this investigation was to determine where more scientific research is needed in the field of IBD, as indicated by the aspects of disease-maintenance about which patients express the most dissatisfaction. Patient testimony unveils gaps in the scientific literature; together these two components can synthesize a more comprehensive narrative of disease etiology and pathogenesis. Determining a more concrete array of causes provides an opportunity to develop treatment methods that may be more efficient and successful in improving patient quality of life.

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Chapter 1

Introduction

The twenty-first century has seen a striking increase in the prevalence of gastrointestinal issues (Adams & Bornemann, 2013). In a 2015 study conducted throughout the United States, it was approximated the cost of treating these gastrointestinal diseases amounted to $7.2 billion dollars (Windsor & Kaplan, 2019). This annual cost will likely continue to increase as the number of patients being diagnosed and requiring treatment rises, in addition to current patients' treatment regimens escalating. The availability of information on any one specific topic within gastrointestinal diseases is still growing due to the more recently increasing prevalence. Inflammatory bowel disease, or IBD, is an autoimmune disorder characterized by disruptions to proper functioning of components of the gastrointestinal tract and other associated physiological systems (Baumgart & Sandborn, 2012). IBD encompasses two subdivisions, Crohn's disease and Ulcerative Colitis. The relative novelty and extensivity of IBD have contributed to a delay in substantiated conclusions about the disease.

The current breadth of scientific literature is limited, and many findings are indeterminant or have inappreciable support to back up conclusions about the causes of IBD and disease activity. Methods of data collection are inconsistent and have yet to sufficiently encompass prospective data. Conversely, patients are directly experiencing the developments of this disease, and have developed their own beliefs of the influence of environmental factors on their disease. Despite the challenges surrounding the current research on these relationships, patient input can be used to supplement science's incomplete narrative. As a driving example, the significance of

stress' role in inflammatory bowel disease remains ambiguous based off research alone. However, the testimony of patients' observations from their own experiences provides insight that helps legitimize the relationship between stress and disease activity. Though the relationship remains indefinite, the validity of the proposal can be strengthened by incorporating patient claims into our scientific understanding.

The purpose of this paper is to bridge the gap between the scientific literature available on IBD and patient testimony regarding their experiences with the disease. Each of these sources were reviewed separately, then synthesized together to construct a more complete narrative. I will start by introducing the methodology of both the review of the scientific literature and the execution of the social media audit. First, the scientific literature will be used to provide background on the causes, pathogenesis, treatment and the inconclusive role of stress. Patient experience will then be investigated by the social media audit. The discussion will then be used to synthesize the respective facets into a more cohesive narrative, followed by a conclusion to direct future research.

Chapter 2

Methods

Literature Review

The growing prevalence of IBD has instigated an increase in research on the functioning of the gastrointestinal tract. To understand the current body of research, I conducted a literature review of IBD etiology, factors involved in the disease pathogenesis and treatment. Elements within the field were investigated as individual components and with overlapping factors contributing to disease manifestation and progression. As studies with similar topics were uncovered, results became more inconclusive. While some studies showed repeated findings, others produced conflicting conclusions. In these instances, the literature was used to synthesize the current narrative. From the synthesis, I focused on the impact of stress on disease activity and flares. This relationship was further examined as a potential focus of treatment to alleviate those effects.

Social Media Audit

Empirical evidence from research is valuable, but may not be sufficient in encompassing the reality of patient's daily experiences with IBD. The intent of the social media audit was to create a patient-based narrative of the disease and its accompanying experiences. Conversations in patient communities were synthesized with, and contrasted with, the knowledge obtained from the scientific literature with the goal of addressing inconsistencies between the two regarding

IBD. Firsthand accounts of patient experience and observations were viewed as supplementary to the findings of empirical research. The patient communities hold the potential to validate the significant role stress plays in inflammatory bowel disease activity. To illustrate this, I examined patient dialogue concerning the role of stress and mindfulness against the scientific literature on the same topic.

I selected Twitter to use as the platform for the social media audit. Twitter is a social media platform that allows users to share written posts of 140 characters or less with the ability to also attach pictures, videos, or links. The initial posts ("tweets") can be shared ("retweeted"), liked ("favorited"), sent to other users individually and replied to (with replies also having the capability of any of the aforementioned actions performed on them). A seed set of terms was utilized to try and encompass users and their commentary on IBD related issues, especially in relation to stress. These seed sets included IBD, Crohn's, Ulcerative Colitis, IBD and stress and IBD and mindfulness. From these searches the most common terms, individuals and topics were noted for use in the next round of searches. I determined the most popular topics and further specified subgroups of each.

Individuals' comments and conversations were organized into six overarching topics: stress, mental health, mindfulness, lifestyle, treatment and physician input. Following these distinctions, the data was continuously reviewed to make specifications of subtopics and develop connections between topics. Upon closer examination, topics were further differentiated. For example, stress was discussed as a cause of a flare, effect of a flare, a target of treatment or a byproduct of failing treatment, and in terms of general stress management.

Table 1. Classification of Themes

Theme	**Subtopics**	**Key Words**
Stress	Cause/Effect of flare, Management	Source, Trigger, Coping, Reduction, Contributor, Cause, Factor, Relief, Mediate
Mental Health	Mind-body connection, Brain-gut axis	Depression, Anxiety, Mood, Emotional Health
Lifestyle	Symptoms, Quality of life	Fatigue, Pain, Sleep, Diet, Brain Fog, Weight Loss, Hospitalization, Exercise, Maintenance
Treatment	Medicinal, Alternative, Novel	Coping, Medicine, Response, Maintenance, Remission, Proactive, Surgery, Resection, Infusions (Stelara, Humira), Adjunct, Complementary
Mindfulness	Preventative, Treatment	Psychological, Yoga, Meditation, Psychotherapy, Wellbeing, Psychogastroenterology
Physician Input*	Support, Objectivity	-

*Physician input was not identified by key words; Instead, it includes users who identify themselves as medical professionals.

Chapter 3

Etiology

Causes

Since much of the research on IBD is indeterminate, it is important to acknowledge the more widely accepted areas of research. Etiology provides some clarity surrounding the role of genetics. Genetic predispositions have been found to be exacerbated by environmental factors, instigating intestinal and immune dysfunction (Zhang & Li, 2014). The variety of physiological systems in which the gastrointestinal tract plays a role is in part why so much of the pathology of IBD is unclear, and more importantly, under-researched. Meanwhile, many risk factors that influence the manifestation of the disease and its symptoms are components of the environment. For these reasons, the pathogenesis of inflammatory bowel disease is indeterminate. Despite the uncertainty surrounding the cause of the conditions that manifest into inflammatory bowel disease, the root of IBD is the occurrence of gastrointestinal malfunction causing inflammation (Matricon et al., 2010). The components of the gastrointestinal tract experiencing this malfunction cause further disruptions to the immune response, as well as intestinal bacteria, epithelial cells, tight junctions and intestinal permeability (Zhang & Li, 2014). Specifically, intestinal permeability alterations lead to invasion and exposure of foreign microorganisms that produce an inflammatory response; As foreign microorganisms cross the intestinal membrane and float freely throughout the body, the immune response is activated (Matricon et al., 2010).

As indicated by IBD's classification as an autoimmune disease, patients suffer from a malfunctioning immune response which triggers inflammation (Richard-Eaglin & Smallheer,

2018). One area of dysfunction due to the defective response of the immune system is the disruption to the epithelial barrier (Zhang & Li, 2014). These disruptions to intestinal homeostasis are especially detrimental in worsening disease severity (Guan, 2019; Zhang & Li, 2014). Increases in intestinal permeability allows foreign antigens to cross the membrane of the intestines (Zhang & Li, 2014). Consistent disruptions to the environment, like those produced by the presence of foreign bacteria, lead to poor metabolism and additional abnormal developments in the gastrointestinal tract (Guan, 2019). The effects of these disturbances increase susceptibility and sensitivity of the intestines to stimuli, which initiates overactive inflammatory responses (Zhang & Li, 2014). While mostly internal biological mechanisms have been identified, the environmental factors inducing the activation of these systems are still to be determined.

Environmental Factors

Despite controversy surrounding the direct effects of environmental factors that cause the initiation of IBD, the literature broadly recognizes the role of a few environmental factors in the disease's progression. Specifically, these effects manifest as further worsening the disease pathogenesis by damaging the already weakened gastrointestinal tract. One environmental factor that has been examined more heavily in research is the use of non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin, by patients with IBD. NSAIDs are not only linked to the exacerbation of IBD but also to progression in disease etiology leading to initial manifestation of the disease (Moninuola et al., 2018). NSAIDs are part of the potential explanation for the development of IBD due to the risk acquired as a result of damage to the gastrointestinal tract (Gupta & Eisen, 2009). Most often this damage is specifically displayed as damages to the

membrane of the small intestine; Damages induce increased intestinal permeability and inflammation, which are defining characteristics of IBD as indicated by the repetitive articulation across literature (Gupta & Eisen, 2009).

While other environmental factors like diet, smoking and prior infection are also discussed, NSAIDs are especially relevant due to the similarity of their role in disease pathogenesis to that of stress. The mechanism of NSAIDs in initiating disease reactivation by increasing permeability is parallel to the mechanism of stress in the body, which produces similar effects on intestinal permeability (Meddings & Swain, 2000). Another important similarity between NSAIDs and stress is the inconsistencies in both between scientific findings and patient experiences. Though Meddings and Swain (2000) recognized the similar biological mechanism the environmental factors stress and NSAIDs acted by, they also noticed that patients did not all experience the same outcome when exposed to either variable.

It is important to note that though these two factors share important characteristics in how they affect patients and their disease, the discussion in literature highlights the differences as opposed to similarities. While both appear to act by similar mechanisms on the permeability of the intestines affecting disease activity, NSAIDs are discussed more definitively. The mechanism they act by and their role in disease activity is more legitimized and conclusive than stress. The certainty is further exemplified by physicians actively addressing the termination of NSAID use in IBD patients. On the contrary, equally distinct recommendations to reduce stress are not made. If both factors show similar biological mechanisms impacting disease, it would be assumed both factors would be accepted with equal significance. Yet, this is not the reality of the literature's interpretation of stress's role in IBD.

Chapter 4

Pathogenesis

Symptoms

Despite the lack of clarity in identifying the specific causes that induce symptoms, the symptoms themselves are discernable. Inflammatory bowel disease is identified as an idiopathic disease, meaning patients experience unpredictable and sporadic increases in disease activity and symptoms (Vilela et al., 2012). These stretches of active disease that interrupt periods of remission are referred to as flares (Garrett et al., 1991). The inconsistent nature of the disease presents a huge obstacle in the determination and implementation of successful treatment, which hinders patient quality of life. Crohn's and Colitis exhibit similar presentations of disease activity, most often as fatigue, abdominal pain, diarrhea, and weight loss due to malabsorption of nutrients in the intestines (Adams & Bornemann, 2013; Baumgart & Sandborn, 2012). These symptoms can manifest across an extremely wide range of severity, from mild to debilitating (Wright et al., 2018).

Remission and Flare-Ups

While it has been determined that some level of inflammation is consistently present even in periods of remission, flare-ups are characterized by elevated inflammation manifesting in increased symptom severity (Wright et al., 2018). Abdominal pain is the most commonly noted flare and primary symptom experienced by patients seeking care (Srinath et al., 2014). As with

many other aspects of gastrointestinal diseases, flare-ups largely have indeterminate causes. This lack of clarity regarding what factors influence flares means it is also uncertain what needs to be targeted in order to successfully induce and maintain remission. Fortunately, some consistencies in the biological mechanisms involved in the inflammatory response have been determined. Based on findings that patients with active disease have elevated intestinal permeability, it was determined that an increase in intestinal permeability increases the probability that a patient will relapse (Welcker et al., 2004). Permeability, in the context of the intestinal membranes is defined as the ability of compounds to cross intestinal mucosa through defective cellular tight junctions (Welcker et al., 2004). This relationship accurately predicted relapse in 76% of patients, making intestinal permeability the most conclusive biological factor contributing to flare-ups (Wyatt et al., 1992).

The interconnected system of components making up the gastrointestinal tract facilitates a domino effect. When one component of the system malfunctions, the effects are widespread, causing other components to break down. Disruption in the intercellular tight junctions is the basis of the leaky gut hypothesis. When tight junctions break down, foreign antigens can penetrate the mucosal walls of the intestine, eliciting an immune response (Ma, 1997). As antigens continue to pass through the damaged membrane, the immune response remains highly activated, initiating the body's elevated inflammatory response. This mechanism is evidence of the role of intestinal permeability in exacerbation and prolongation of intestinal inflammation precipitating a flare (Ma, 1997).

It is hypothesized that the overlap among intestinal permeability, the immune response and inflammation share another related element, and that is stress. One theory suggests that the physiological mechanisms of the stress response interact with aspects of the immune and

inflammatory responses. If supported, this association could be used to justify implementing treatments that target one of the affiliated components, for example intestinal permeability or stress, in order to mitigate inflammation and symptom severity.

Inflammatory Bowel Disease

IBD has become a topic of increasing concern as its prevalence throughout society has increased. Due to the novelty of gastrointestinal diseases, and the comparably short time span with which they became widely recognized among society, a consensus has yet to be reached on the current multifactorial etiology. Inflammatory bowel disease is a term encompassing diseases causing inflammation and dysfunction in different parts of the gastrointestinal tract that most commonly manifests in abdominal pain (Greene et al., 1994). Inflammatory bowel disease differs from irritable bowel syndrome, also known as IBS. This difference is of importance to note because though IBD and IBS patients may experience some of the same symptoms, IBS is diagnosed clinically, by ruling out other potential diseases since there are no visual biomarkers for confirmation (Canavan et al., 2014; Chey et al., 2015). On the other hand, IBD diagnosis requires examinations and procedures ordered by a physician (Crohn's and Colitis Foundation, n.d.; Srinath et al., 2014). Both internal and external factors are receiving equal investigation as causes of the disease, from genetic origins to explanations of diet, prior infection, and smoking. IBD specifically refers to Crohn's disease, which affects the small and large bowel that makes up much of the intestinal tract, and Ulcerative Colitis, which is found in the colon and rectum (Greene et al., 1994). Current research is spread sparsely between theories, weakening significance and leaving the underlying mechanisms of disease etiology up to debate. Despite the

variety of potential risk factors considered to be at play, each face contrasting evidence that further diminishes the validity of the proposed pathways.

Chapter 5

Stress

Stress affects multiple major pathways in the body, including the central nervous system, the autonomic nervous system, the immune system and the gut. Stress is defined as any threat to a host's homeostasis that requires physiological or behavioral reaction to maintain homeostasis (Greene et al., 1994; Mawdsley & Rampton, 2005). More specifically, psychological stress specifically refers to when an individual perceives environmental demands as being taxing, especially to the point of exceeding their adaptive threshold (Srinath et al., 2014). Though defining stress can be complex as it is used in reference to such an array of circumstances, there is a basic underlying physiological response mechanism that is followed.

The Central Nervous System encompasses many components that are susceptible to experiencing effects of the stress response. The body's hormonal response to stress is regulated by corticotropin-releasing factor, or CRF as part of the hypothalamic-pituitary-adrenal axis, or HPA axis (Smith & Vale, 2006). CRF is the first to respond to stress by initiating the release of adrenocorticotropic hormone (ACTH), which mediates the action of glucocorticoids in regulating processes like the immune response (Smith & Vale, 2006). These shared molecular components generate a feedback loop between immune cell function and activity of the HPA axis is (Srinath et al., 2014). Through these mechanisms, stress presents a biological relationship to the immune response.

Another important process affected by stress is the brain-gut axis which associates the enteric nervous system within the gut to the sympathetic and parasympathetic divisions of the

autonomic nervous system in the brain and spinal cord (Mawdsley & Rampton, 2005). This interaction allows neurotransmitters released by the brain to affect inflammatory cells at cell junctions within the gastrointestinal tract (Mawdsley & Rampton, 2005). An example of this process is illustrated by the immunosuppressive effect of glucocorticoids involved in the HPA axis (Mawdsley & Rampton, 2005). Other elements of the gut that are vulnerable to the body's response to stress include substance P and associated mast cells. Substance P relays a signal that enhances production and stimulation of inflammatory cells and causes mucosal inflammation which mast cells attempt to mediate before permeability is affected (Mawdsley & Rampton, 2005). These associations are important to be familiar with in order to understand the extent of the body's response to stress, and the array of components involved.

Connection to Inflammation

Studies have begun to uncover the impact of stress on immunosuppression, autonomic and enteric nervous system variations and intestinal permeability leading to inflammatory responses within the gastrointestinal tract (Bonaz & Bernstein, 2013; Wynne et al., 2019). Aside from direct consequences experienced in the gastrointestinal tract, stress also impacts an individual's immune response. Increasing stress hormones, specifically cortisol, epinephrine and norepinephrine, throughout the body inhibits immune cell function by acting through the sympathetic nervous system (Bonaz & Bernstein, 2013; Mawdsley & Rampton, 2005). As components of the immune response are inhibited, the HPA axis also induces intestinal permeability and allows antigens to cross the membrane, which increases intestinal inflammation (Bonaz & Bernstein, 2013). Intestinal permeability has been identified as having a dose response relationship with stress; The more the body must respond to stress, the more permeable intestinal

walls become, which increases exposure to foreign invaders, continuing the damaging cycle (Bonaz & Bernstein, 2013).

It should be noted that data in support of the relationship between intestinal permeability and the initiation of inflammation in manifestation of symptoms has been found consistently among literature for over a decade (Ponder & Long, 2013). These confirmed associations help to validate the predicted significance of stress's effects through the presence of corresponding components.

Time

As it has been noted that stress is a term used in varying capacities, it is important to differentiate between circumstances and their outcomes. Stress experienced during developmental stages of early life has the potential to produce long term effects on the body's stress response mechanisms (Srinath et al., 2014). These effects may then influence future experiences related to stress. Adaptions by response mechanisms to stimuli create new baseline threshold levels, which in the context of chronic diseases like IBD may translate to alterations in the perception of symptoms (Bonaz & Bernstein, 2013).

Differences in the duration of time stress is experienced can also produce variable physiological responses within an individual. Specifically, chronic stress results in prolonged elevated cortisol levels, producing an exaggerated response to instances of acute stress which contributes to immunosuppression (Mawdsley & Rampton, 2005). Experiences labeled as spontaneous, acute stress are predominantly experienced. One advantage of acute, daily stress is that it is more immediate and identifiable and thus an easier target for treatment interventions. An important aspect of the effects of stress on physiological manifestation of symptoms is that

this relationship has been noted as expressing bidirectionality. Not only does an increase in stress increase symptoms but a decrease in either variable decreases the experience of the other (Sexton et al., 2017). In addition to these effects of stress being reversible, they can also be mediated. Many measures that analyze the physiological effects of stress on the body are subjective; The severity of stress an individual reports experiencing is largely based on their personal judgement. A cross sectional study conducted by Garrett and colleagues demonstrated that more symptoms were experienced by individuals who also reported perceiving higher levels of daily stress (Garrett et al., 1991). Science has noticed that an individual's perception of stress can decrease their threshold of sensitivity to future stress; Increasing frequency of experiencing stress and thus the likelihood of an inflammatory response (Mawdsley & Rampton, 2005).

Perception

How individuals perceive stress is important because if the perception of stress and thus the body's response can be mitigated, the effects of the response mechanism could be alleviated. The most negative effect of reported high levels of stress is the reduction of the individual's pain threshold (Mawdsley & Rampton, 2005). The relationship between increased perceptions of stress on decreasing pain thresholds helps to explain elevated severity of symptoms during periods of high perceived stress (Sexton et al., 2017). With these relationships uncovered, symptom severity could be reduced by perceiving stress at a lower gradient, specifically in relation to an individual's threshold. In other words, reduction in biological malfunctioning and manifestation of symptoms could be achieved through controlling stress perception. This potential role in symptom reduction would allow this process to be used for a target of future

treatment. An example of a treatment that aligns with this methodology is mindfulness-based interventions, which teaches patients to perceive stress differently and regulate their physiological responses to manage disease activity and symptoms.

Stress perception has been deemed relevant to the discussion regarding IBD, but there are more in-depth mechanisms to examine to understand the significance. While the brain structure of IBD patients alters in response to processing undesirable stimuli, variations occur independent to the severity of inflammation (Srinath et al., 2014). As inflammation is determined as only one cause among other factors affecting an individual, the role of cognitive processes is uncovered (Srinath et al., 2014). The relevance of these processes is that, like the immune response, the psychological mechanisms are under an increased risk of dysfunction among patients with IBD (Neilson et al., 2015). Furthermore, psychological transformations specifically can be tied to symptom perception (Srinath et al., 2014). While physical pain, like abdominal pain, is noted in IBD patients as indicative of disease activity, the perception of pain without physical manifestations suggests another factor is facilitating the pain experience (Reed-Knight et al., 2018). For example, one study concluded that experiences of disease manifestations could be predicted based on coping style; inferior coping styles were predicative of increased frequency of negative experiences (Mussell et al., 2004). In a study conducted by Mawdsley and Rampton (2005), the role of perception in identifying the significance of stress experienced by a subject was examined objectively using a perceived stress questionnaire. Individuals reporting in upper divisions of the distribution of stress perception were associated with patterns of mucosal membrane dysfunction, increasing their risks of worsening symptoms (Mawdsley & Rampton, 2005).

Like biological mechanisms, psychological processes follow a specific progression. Bonaz and Bernstein (2013) conducted a study that produced a significant finding in support of the potential of mindfulness-based interventions by demonstrating the relevance of individual's mental processes. Their study outlined the role of the placebo effect in IBD activity experienced by patients (Bonaz & Bernstein, 2013). They were able to uncover evidence that portrayed how disease activity could be influenced by factors independent of interaction with the body, such as stress (Bonaz & Bernstein, 2013). The relationship that patients' own expectations can manifest into biological responses is valuable. For example, an individual's experience of stress may be correlated to their interpretation of pain, which supports the argument that altering patient perceptions of stress can affect their disease experience (e.g., pain) and clinical response.

Chapter 6

Treatment

Prognosis/ Therapy

As the literature on IBD grows to establish a more complete picture of etiology specifically, there is the potential for novel treatment options that mitigate clarified causes of symptoms. In early treatment development, 80% of Crohn's patients received surgery and up to a third of UC patients required a colectomy (Vilela et al., 2012). Still, today 50% of Crohn's patients require surgery within 10 years of their diagnosis (Wilkins et al., 2011). Another form of treatment includes drug therapy. Mild drug therapy uses anti-inflammatories and antibiotics, while stronger corticosteroids are implemented for more severe disease activity; Stronger still, and the highest step in pharmaceutical treatment, are biologics which are administered most often as injections or infusions (Pithadia & Jain, 2011).

The goal of IBD treatment is to reduce symptoms, induce remission and sustain decreased disease activity (Wilkins et al., 2011). The first step of controlling symptoms can be decided according to disease location and severity. What is referred to as a step-up approach is employed, meaning treatment starts with the least intrusive method and progresses in intensity with disease activity (Pithadia & Jain, 2011). Though current primary therapies are pharmaceuticals, medicine still has barriers that impact the success of treatment. The goal of most medicines is to control the overactive immune response to initiate and maintain remission (Wright et al., 2018). The problem with the goal of treatment being maintenance of symptoms specifically, is that escalation of treatment is inevitable since the underlying disease itself can

continue to progress. Additionally, worse symptoms are often experienced upon removal of interventions (Pithadia & Jain, 2011). The inability to assure longevity of most treatment options is not ideal, especially since IBD has no cure. These drawbacks emphasize the importance of establishing a greater knowledge of IBD etiology so more efficient and lasting treatment options can be developed.

While research on IBD specifically is still limited, the literature on chronic diseases and their treatment options has expanded. IBD patients have similarly begun to voice an interest in the implementation of alternative forms of therapy, specifically forms that can be utilized on their own accord, like behavioral therapies. This amount of perceived control could give patients a feeling of greater self-efficacy in managing their disease, which has been found to help decrease stress (Arruda et al., 2018).

Mindfulness-Based Interventions

Patient inquiry about alternative treatment mechanisms is not unreasonable. An important study revealing the inconsistencies between heightened symptoms and the presence of biomarkers indicative of disease activity demonstrated the need to expand the scope of treatment mechanisms of IBD (Bonaz & Bernstein, 2013). One way to expand treatment could be by utilizing psychological based interventions. Although controversial, some studies have produced findings indicating that among inflammatory bowel disease patients, when perceptions of stress are affected, so is their symptom experience; To the extent that the perception of stress significantly affected the initiation of symptoms (Bernstein et al., 2010).

One form of alternative therapy that has recently increased in popularity is mindfulness. Mindfulness is defined as being intentional, focused, and present without judgement in order to initiate physical and mental changes that improve well-being (Hood & Jedel, 2017; Neilson et al., 2015). In order to produce the desired physiological benefits, the autonomic nervous system and immune system are targeted by the intervention (Hood & Jedel, 2017). The intended changes necessary to induce wellbeing are often based in mental processes affected by stress, anxiety, depression and pain perceptions (Hood & Jedel, 2017).

As with pharmaceuticals, the goal of mindfulness-based intervention is to reduce symptoms, which is done by implementing coping strategies to diminish the physiological consequences initiated by stress (Grossman et al., 2004). An incomplete understanding due to limited research has created controversial stances supporting psychological therapies, like mindfulness-based interventions as treatment for IBD. Despite the limitations establishing the direct effect of mindfulness on IBD activity, mindfulness-based interventions do have support regarding their use in the reduction of stress (Neilson et al., 2015).

The hypothesis of implementing mindfulness therapies in order to stimulate the body's parasympathetic nervous system to reduce symptoms has been identified in multiple studies (Bonaz & Bernstein, 2013). The goal of monitoring and recognizing emotional responses to situations is so individuals can identify triggers and response patterns that need to be resisted in order to activate the parasympathetic nervous system (Nielson et al., 2015). A study incorporating patient testimony demonstrated that though the scientific community may be inconclusive about the role of psychological therapies, patients recognize and express the benefits of learning how to implement coping strategies to reduce their symptom severity (Jordan et al., 2018).

One of the most common mindfulness practices is yoga, defined as a mind-body discipline that incorporates posture and breathing techniques with the intention of decreasing sympathetic nervous system activity and increasing parasympathetic nervous system activity (Arruda et al., 2018). The positive effects of yoga surpass reducing perceived stress and disease relapse. Yoga gives patients self-awareness and self-efficacy through providing more knowledge and control over their disease maintenance (Arruda et al., 2018; Hood & Jedel, 2017). In addition to yoga, meditation also improves awareness of the body and its response to stimuli, like stress (Hood & Jedel, 2017). Though correlations are seen, the relationship likely needs to demonstrate significance across the literature before physicians are willing to support and implement these interventions. In a primary research study conducted in 2019, differences between a control and intervention group of undergraduate students using a meditation app daily were significant and permanent enough to still be detectable at follow-up, demonstrating that mindfulness activities can reduce stress, even prospectively (Huberty et al., 2019). Additional support was illustrated in a metanalysis that found mindfulness-based intervention to be applicable and effective across daily events and severe circumstances, benefitting physical and mental wellness (Grossman et al., 2004). Though there is still no consensus regarding the usefulness of these interventions, the benefits illustrated by studies finding significance offer a promising evolution in IBD treatment and patient quality of life.

Chapter 7

Social Media Audit Analysis

Patients' perceptions or experiences surrounding their disease can vary from scientific views regarding the disease. For this reason, patients have some different viewpoints concerning the initiation of inflammation and disease activity than scientists have developed through research. The firsthand experiences of patients may be invaluable to gaining knowledge on the course of IBD, despite the information being attained from their natural, uncontrolled environment. Additionally, while the impact of stress on IBD activity and flares was the focus, mindfulness was used to highlight the hypothesized significance of stress on IBD. The social media audit was also constructed to encompass a variety of understudied topics that contribute to the incomplete picture surrounding inflammatory bowel disease.

Tweets were categorized as mental health if they mentioned comorbid issues with anxiety or depression. Mindfulness was referred to in terms of a preventative tool, a treatment, and in relation to stress, mental health issues and severity. Lifestyle was talked about in terms of symptoms and quality of life, especially referencing disease interference with daily activities and quality of life. Dialogue about treatment was discussed through sharing experiences with medicinal treatment and patient solicitation of alternative or new therapy options. Physician input was classified as tweets by users who identified themselves as a doctor in their handle, username or biography on their profile. Identifying subtopics allowed for more explicit overlap between themes so a greater intertwined narrative could be composed. Tweet collection was continuous to ensure up to date input was included. Upon reviewing the collection of tweets, I

synthesized the patient experience presented via Twitter. Of the identified subtopics, I focused on mindfulness to exemplify the importance of filling the current holes in research, specifically regarding the hypothesized significance of stress.

Patient's experiences with IBD are important to recognize due to the wide range of effects this disease has on their daily lives. Some patients expressed an apprehension to participate in certain activities, like trying new foods or traveling or avoiding activities before symptoms are even present. Yet, these activities overlap as important elements of disease maintenance, for example with respect to diet. While one patient shared being nervous to try a new recipe, another cited diet as a determining factor in achieving remission.

> "...we're trying vegetarian meal delivery services... I'm nervous abt this b/c of my crohns..." (@PinkieAvalon, https://twitter.com/PinkieAvalon/status/1354564639959334913?s=20).
>
> "...seems to me the best avenue for med-free maintenance of remission is diet & lifestyle changes..." (@IldikoMe, https://twitter.com/rowforfun/status/1298256964858740736?s=20).

Another aspect of IBD affecting the lives of patients includes the financial burden of treatment. While some patients express dissatisfaction with the success of medication, or declare a need for novel methods, many patients voice a concern with the cost. Though this issue was discussed to a smaller degree compared to other topics it was still emphasized by those who experienced it. One tweet made by a user who mentioned reaching her out-of-pocket max received surprisingly high engagement considering the relevancy of the topic was not widespread, with 6 replies, 1 retweet and 41 likes (@ownyourcrohns, https://twitter.com/ownyourcrohns/status/1354648264247799809). The extent of IBD's

concealed role across patient's lives is important to acknowledge so it can be contained. Experiences associated with symptoms and treatment are just a few examples.

The connection between emotional and physical health, called the mind-body connection, or in the context of IBD, the brain-gut axis, is receiving increasing attention from both the scientific and patient communities. The difference between conversations about the connection is that patients perceive it to be fact, while physicians remain more objective without sufficient evidence. Some physicians seem to recognize the potential of intervention strategies based in mindfulness. Although they refrain from accepting the relationship without empirical evidence, some physicians do express optimism.

> "Excited that finally we're talking about brain-gut connections…It's a complex interaction we're barely understanding…" (@LindaNguyenMD, https://twitter.com/LindaNguyenMD/status/1024035631788216321?s=20).

Patients believe the connection to be a cycle. Their perception of the cycle induced by the brain-gut axis draws connections from anxiety, to stress, to symptoms, to depression and back around while the intensity of the experience builds.

> "It's a vicious cycle. Anxiety seems to impact my UC, I then get stressed out that my UC is getting worse, depression increases, stress/anxiety increases, rinse, repeat." (@KatInouye, https://twitter.com/KatInouye/status/1116016253234061313?s=20).

As patients observe new cause and effect relationships influencing flares, new potential targets of interventions are uncovered that could expand the success in treating patients.

Insufficient treatment has driven patients to express desire for implementation of other forms of treatment. Patients are not only voicing when treatment is failing, but the directions in which they are looking for treatment to evolve. Patients recognize the potential for other intervention options and express enthusiasm to explore them. One patient referencing alternative therapies, specifically cognitive behavioral therapy, tweeted:

> "I'm hearing more and more about this therapy and it's making me want to go for it. I don't know what's holding me back…" (@Empoweringpts9, https://twitter.com/Empoweringpts9/status/1118366978899628032?s=20).

The desire and recognition of complementary and alternative treatments speaks volumes to the integrity of patient claims. Patients perceive benefits of utilizing multiple types of therapy, both medicinal and behavioral.

> "…Id love a program that goes along side chronic illness… #dreamingforthefuture" (@louisehelenhunt, https://twitter.com/louisehelenhunt/status/1118601012640612354?s=20).

Though patients convey a desire to explore alternative and novel treatment options, their reluctance in requesting these interventions may be due to a lack of support, guidance or information that they express feeling from their physician. This disconnect between patient and physician is not only present in discussions regarding treatment, but also in identifying the believed causes of disease activity that need to be treated.

While acknowledging the insufficient and inconclusive research regarding the connection between stress and IBD disease activity, patients report much more decisive conclusions. Not only do patients recognize the role of stress, but they often feel very strongly and definitively that it initiates symptoms. Many individuals shared their efforts to avoid stress.

"@sarckybas try as much as possible to not get stressed out as that will cause the crohns to flare up" (@Dynamomagician, https://twitter.com/Dynamomagician/status/1314731463678402 58?s=20).

In addition to their emphasis of the importance of reducing stress due to its initiation of flares, patients also noted the bidirectionality of the relationship. Patients want to avoid stress due to their belief in its ability to induce flares and because they perceive that flares pose a threat by enabling stress and prolonging the increase in disease activity.

"It can be a vicious circle, stress worsens #IBD and flare-ups worsen stress... It's difficult to break." (@theblisser, https://twitter.com/thebissler/status/601831874395303936?s=20).

However, when discussing their experiences that recognize stress as a factor in disease activity, patients perceive their physicians to be hesitant.

"My consultant says no but I know stress is my main trigger." (@TruthsterThe, https://twitter.com/TruthsterThe/status/1117524679865008130?s=20).

Conversations between patients likely benefit from the absence of a physician by providing individuals with an opportunity to speak openly. Patients convey feeling that their input is not valued by physicians when relaying their experiences to insinuate other, potentially more successful treatments. Regardless of physician beliefs, their experiences speak for themselves.

"…I have had flares whenever under stress, worry, anxiety. I believe if mind is at rest body also follows it." (@Kanchan_warrior, https://twitter.com/Kanchan_warrior/status/1248974802603278337?s=20).

Across patients' perspectives, their experiences with mindfulness proved successful enough to recommend to other patients. Patients do recognize mindfulness is not the cure, but positive outcomes are beneficial enough to pass on the knowledge of the experience and encourage others to try.

"… My tips are more mindfulness…" (@radmore999, https://twitter.com/radmore999/status/1257452083609055233?s=20).

Mindfulness is recognized as advantageous through affecting multiple states of disease activity. While the success of mindfulness was referenced by patients when implemented as a preventative measure to manage symptoms, it was also perceived to reduce stress that may have been present.

"… Currently free of symptoms and manage the illness through diet and mindfulness (well when possible)." (@Pixie1303, https://twitter.com/Pixie1303/status/1133118647281565697?s=20).

"Did yoga… Bc I was flaring-up all morning w/ my ulcerative colitis…" (@cnhedrick, https://twitter.com/cnhedrick/status/1354941447129108488?s=20).

Patient anecdotes involving mindfulness had notes of optimism, satisfaction, and the recognition that success is not guaranteed, as exemplified when the aforementioned user referred to her success using diet and mindfulness being limited to when possible.

An interesting component of this audit was the presence of physicians and their contributions to patients' commentary. Physicians expressed support to patients' claims regarding factors causing disease activity, the need for more research and alternative treatments,

despite patients' perceptions of physician's skepticism in clinic. Physicians openly acknowledged shortcomings in science and their accompanying gaps in the field of medicine:

> "Majority of IBD patients report a relationship between stress, emotion, food and the severity of their GI symptoms, yet these factors haven't been addressed by research/clinical community until recently." (@emeranamayer, https://twitter.com/emeranamayer/status/955602688602923008s=20).

> "The GI world... is catching up with our patients in finding the chemical and neuronal changes caused by stress..." (@JeanneTungMD, https://twitter.com/JeanneTungMD/status/1055552845536264194s=20).

An even more impressive perspective was that physicians advocated for additional forms of treatment. In addition to their alignment with patient beliefs, they justified patients' pursuit of alternative treatment methods.

> "...A global reality that stress and depression are common in #IBD Should be managed with same rigor as the othe extra intestinal manifestations. Important to include psychology/psychiatry..." (@MRegueiroMD, https://twitter.com/MRegueiroMD/status/1193069385277153285s=20).

In addition to its presentation of patient experiences and perspective, the audit included the presence of physician input. While the expression of patients' beliefs was helpful in supplementing the gaps in science, and in identifying popular topics of concern, validation by physician support added an additional component to the narrative. Patients' testimony regarding IBD's effects on lifestyle, the relationship between mental processes, like stress on disease activity, and their eagerness for novel treatment methods were all endorsed by physicians.

Chapter 8

Discussion and Conclusions

Discussion

Analyzing patient conversations provided an invaluable perspective to the current knowledge surrounding IBD. The enthusiasm patients express in hypothesizing factors affecting their disease indicates their desire to have an active role in their disease. While content obtained from the dialogue may not be applicable to clinical settings, it does provide direction for deeper examination by the scientific community.

While the brain-gut axis has been discussed in the scientific community, its effect as a whole and as isolated components remains tentative. However, patients have expressed noticing effects they refer to as mind-body connections, and even noted the bidirectionality of the relationship. The incorporation of anxiety and depression highlights the aspect of mental health that patients use widely in conversation regarding their disease. Unfortunately, science has thus far failed to shed much light on the topic as it relates to IBD. The bottom line is that these factors that are believed to affect symptom activity all play a role in patients' quality of life. In addition to pain, patients reported a variety of other symptoms that tend to have effects significant enough to interfere with activities of daily life. If symptoms can be reduced and daily tasks can be completed more successfully, a patient's overall quality of life can benefit.

Most treatments of chronic disease aim to minimize the severity of the disease to increase the quality of life of the patient. Despite deficiencies in literature regarding the relationships between stress and IBD flares, there is a growing field surrounding mindfulness and stress. The

latter, more substantiated association can be used as the basis in support of mindfulness-based interventions treating IBD. Observing personal experiences has driven patients to express a strong belief about the role stress plays in initiating increased disease activity. The decisiveness among the patient community, even without support from physicians or the scientific community, should be a driving force in prioritizing the investigation of this research by the scientific community. Based on the potential association between stress and flares noted in the literature, conclusiveness among patients supports the utility of mindfulness therapy to reduce stress and indirectly reduce flare-ups (Sun et al., 2019). The implementation of mindfulness-based intervention to treat IBD has not been addressed sufficiently by scientific literature to be prescribed by physicians. However, there is a growing field of research investigating the effects of mindfulness-based intervention on reducing stress. The underlying mechanisms are still undetermined, but there have been findings supporting the success of mindfulness therapies in stress reduction (Pascoe et al., 2017).

Regarding physician response, outside of a clinical setting, health practitioners voice a recognition and awareness of patient claims. Their hesitation to act in support of these assertions is likely due to the lack of substantial evidence. Without enough data establishing the observed relationships, physicians must adhere to values of the scientific community and not assume correlation is indicative of causation. In this way, both physicians and patients are disadvantaged by the inconclusive pool of research. Despite the current dissonance between communities, the shared burden from the current limitations may explain the support expressed by physicians within the patient community online. Physicians likely advocate for the importance of pushing for more research on these topics so they can more successfully fulfill their role in serving

patients, especially, since patients appear eager to have an active and collaborative role in their disease management.

Though science seems to be on the right track by noticing the potential relationship between stress and IBD disease activity, patients appear to have developed a more concrete connection and feel it is substantial enough to be recognized as a specific part of treatment. While the relationship between stress and IBD is not empirically supported, the potential benefits of identifying an additional cause that could be used as a target for treatment warrants progression of research. Patients' appeal for progressive therapy was expressed explicitly, often by conveying dissatisfaction with the treatment options available and testimony of failed treatment. Many practitioners taking part in patient conversations voice support of these claims. While the root of the hypothesis specifically regarding stress is not substantially supported with evidence, the possible benefits of uncovering more causes warrants action to be taken. The scientific community needs to be put under more pressure to elevate the priority of this research. Doing so will allow necessary measures to be taken to strengthen the understanding of the relationship between environmental factors, like stress, and disease severity. With more solidified causes determined, more targets for treatment may be utilized to develop novel methods.

Limitations and Future Directions

Limitations in the Research

An important step in producing more influential contributions to science is by first identifying the shortcomings and opportunities for modification and improvement. Insufficient

data is delaying progressive treatment from being widely trusted and implemented. This is cause for concern because it is intervening with patient wellbeing and success in disease management. Though there are promising and suggestive findings that effects of mindfulness-based interventions could manage symptoms of inflammatory bowel disease, incompetent studies limit the implementation of this therapy for treatment (Srinath et al., 2014). One of the most significant weaknesses across available studies is that they are retrospective. A downfall of retrospective studies is the increased risk of researchers collecting inaccurate data that may mislead findings (Greene et al., 1994). Inaccurate data is never favorable, but when findings on a topic are already inconsistent and studies are rare, this flaw is especially likely to go unnoticed, skewing results likely to be used in comparisons with future studies. Disease progression, remission, and relapse, all require prospective studies to determine patterns of the disease. Prospective studies are most effective in determining how one variable affects another, time which provides important information regarding longevity of therapies and long-term outcomes.

Two other additional study designs that could be especially relevant and successful to research on IBD are ecological momentary assessments, or EMA, and self-experimentation studies. EMA and self-experimentation are both studies that evaluate subject's real-time experiences in their innate environment to maximize the efficacy of results (Heron & Smyth, 2010). EMA and self-experimentation are both studies that evaluate subject's real-time experiences in their innate environment to maximize the efficacy of results (Shiffman et al., 2008). This type of data collection is often conducted through mobile technological devices and forms of daily or weekly diaries, so patients have detailed reports of experiences that are likely void of recall bias (Shiffman et al., 2008). These study designs provide an opportunity to quantitatively measure patient's claims (Karkar et al., 2016). Additionally, these methods may be

especially applicable to noticing patterns of flares and remission and especially, in recognizing elements inducing flares. Considering the push for information on IBD, this form of data collection and analysis may prove to be extremely valuable in determining the factors that affect an individual's disease and in applying the information collected in these personal circumstances to create progressive forms of intervention.

Defining and measuring a subjective variable like stress can attribute to inconsistencies in data collection and analysis. In evaluating daily experiences of stress, a retrospective study will not be able to accurately recount each experience initiating a stress response, producing recall bias. Additionally, the definition of stress is important to hold consistent so data collected on physiological responses can be standardized and compared more effectively. Fundamentally, studies need to be more structured; Methods and measurements need to be more specific and universal; Sample sizes need to be larger so findings can be generalized across the population, and, subjects need to be retained throughout the study. To fix these shortcomings and produce a more complete base of knowledge about IBD, this area of research will require money and time. Though there is clearly a relationship between individuals' genes and environmental factors that plays a role in disease etiology and pathogenesis, the specific mechanisms of potential factors are currently uncertain. Until there is more conclusive evidence surrounding the interaction of factors affecting IBD, treatment cannot progress appropriately.

Future Directions

Though there are limitations impairing the data currently available, recognizing and addressing these shortcomings provides opportunities to explore different directions to produce more accurate, representative and useful findings. In the case of gastrointestinal issues, future

research needs to be more extensive. There are many aspects of mental and physical health that pertain to IBD. As in the examples of stress and mindfulness, there is a disconnect between the literature and patient testimony regarding the relationships between factors. However, before alternative treatments can be integrated, the underlying mechanisms of factors inducing disease manifestation and activity need to be conclusive. It is especially important to determine the accepted causes of IBD as it is an idiopathic disease, and severity experienced by patients ranges across such a wide spectrum. Discovering new treatment strategies essential to increasing patient satisfaction and relief from disease symptoms may likely leads to elevating their quality of life.

Conclusions

Ultimately, future research needs to produce a more comprehensive literature on the factors contributing to IBD. Once the components effecting IBD are accepted, reducing disease activity and improving patient quality of life through treatment can be more efficient. Despite the inconclusive association between stress and flares in scientific literature, patients demonstrate a more consistent experience with stress and their disease activity, as outlined by the findings of the social media audit. This documented relationship between experiencing stress and an increase in IBD activity supports the potential of mindfulness-based interventions and the use of coping mechanisms to mitigate the negative effects of the stress response. This type of treatment would be beneficial by decreasing severity of disease activity and symptoms through the regulation of individuals' perception of stress.

Defining the specific relationship between stress and IBD could aid in more successfully treating patients. One example was shown by minimizing perceived stress through implementation of mindfulness-based interventions to decrease disease activity. According to

noted and supported physiological mechanisms, suppressing the body's response to stress might control the overactive immune response that induces inflammation in patients with IBD. While the body of research on inflammatory bowel disease is still growing, patient testimony exemplifies the burden of this failure in science on improving patient's disease experience and quality of life. However, with progressive future research there is ample opportunity to mend the disconnect between the narratives of science and patients in order to more successfully treat IBD.

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ACADEMIC VITA

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Education

2019- Present	Schreyer Honors College
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2012-2017	Pennridge High School Top 10% of Class

Experience

Alpha Epsilon Delta- Pennsylvania Beta Chapter Spring 2019- Current

Honors Society prepares members for future as health professionals

Wear-It: Real Time Science in Real Life Research Lab January 2019- Spring 2020

Utilization of cutting-edge technological advances to collect real time data and implement immediate intervention, specifically to patients of addiction.

Shadowing at University of North Carolina Chapel Hill Summer 2019

Shadowed Otolaryngologists in clinic and the operating room, interacted with health professionals and patients.

THON 2017- 2020

FOTO Special Interest Organization Member- 2017-2018

- Participate in actively fundraise, attend events to fundraise and attend final event

Rules and Regulation Committee Member- 2019

- Trained to execute safety and security at event, inform event participants of rules, fundraise year round

Dancer Relations Committee Member- 2020

- Trained to care for physical and mental health of individuals dancing 46 hours, fundraise year round

Honors and Awards

Dean's List	Fall '17, Spring '18, Fall '18, Spring '19, Spring '20, Fall '20
Scholar Athlete Award Women's Lacrosse	2017
National Honors Society	2016-2017
Distinguished Honor Roll	2013-2017