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Advancements in Immunomodulatory Therapies for IBD and Their Interplay With the Gut–Brain Axis: An Updated Review of Current Literature and Beyond

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ABSTRACT

Background and Aims: The incidence of inflammatory bowel disease (IBD), characterized by chronic gastrointestinal inflammation, has significantly increased over the last two decades. Concurrently, advancements in treatment strategies have accelerated, aiming not only to induce but also to maintain remission. Emerging evidence highlights the intricate bidirectional relationship between the gut and brain, forming the gut–brain axis, which is now a major therapeutic target.

Methods and Results: This narrative review synthesizes findings from a wide range of research studies to summarize IBD incidence trends, underlying pathophysiological mechanisms, and recent therapeutic advancements. A major focus is placed on dysregulated immunomodulation and its role in disease progression. The review examines conventional treatments such as aminosalicylates and corticosteroids, surgical interventions, and newer therapies targeting the gut–brain microbiota axis, including biological agents, stem cell therapy, probiotics, and fecal microbiota transplantation (FMT).

Conclusion: Recent advancements in immunomodulatory therapies have significantly improved patient outcomes. Biological agents such as infliximab and vedolizumab have demonstrated remission rates of 40%–69% in IBD patients, with infliximab reducing colectomy. Rates to 10% at 54 weeks. Meanwhile, fecal microbiota transplantation (FMT) has emerged as a promising therapy for ulcerative colitis, with trials reporting 87.1% clinical remission at 48 weeks compared to 66.7% in the placebo group, along with higher endoscopic and histological remission rates. A trial on multidonor-intensive FMT found a 27% clinical remission rate at week 8, significantly higher than 8% in the placebo group, reinforcing its potential as an adjunct therapy in IBD. By examining their interplay with the gut–brain axis, this review provides insights into the mechanisms and clinical relevance of these therapies, paving the way for more targeted and effective IBD management strategies.

1 | Introduction

Inflammatory bowel disease (IBD) presents a significant challenge in modern healthcare due to its chronic nature and unpredictable course. Diarrhea, abdominal cramps, anemia, weight loss, and fatigue often characterize it. With its rising global prevalence, effective management strategies are imperative as they threaten the patient's well-being and cause financial burdens to the families [1, 2]. The etiopathogenesis of IBD is not thoroughly understood, although multiple factors involving genetic modifications, host immune dysfunction, intestinal dysbiosis, and environmental effects have been implicated [2]. There has been an increase in the number of options available for the treatment of IBD within the last 20 years, and newer therapies are proving to be successful in many patients. Conventional treatments control symptoms through pharmacotherapy, surgical interventions are successful but cause remission in most patients, and the newer treatment modalities that target the gut–brain axis and stem cell therapy have proven to induce remission and sustain it. However, the treatment does not seem to be fruitful in all patients. Therefore, there is a need for new strategies, treatment combinations, and additional therapies to cater to all patients of IBD [1, 3]. In this review, we have enumerated the multiple probable pathogenesis theories for IBD, listed the latest research on emerging pharmacotherapies, and discussed the target sites of newer therapies.

2 | Methods

2.1 | Literature Search

We conducted a comprehensive literature search across PubMed, Google Scholar, Scopus, and Web of Science to identify seminal and recent articles on immunomodulator advancements, emerging Inflammatory Bowel Disease (IBD) therapies, and their interactions with the gut-brain axis. Special attention was given to studies published within the last 5 years to ensure the inclusion of the most up-to-date research findings. Keywords used in the search included “gut-microbiota-brain axis”, “IBD management”, and “psychological stress and IBD”, among others relevant to the scope of this review.

2.2 | Selection Criteria

To ensure a systematic and reproducible approach, articles were selected based on predefined inclusion and exclusion criteria:

- Inclusion criteria:
  - Peer-reviewed original research articles, systematic reviews, and meta-analyses focusing on IBD treatment, immunomodulatory therapies, and gut–brain axis interactions.
  - Clinical trials and cohort studies with a sample size ≥ 30 to prioritize statistically robust findings.
  - Studies published in English, though pivotal research in other languages was considered if English translations or summaries were available.
- Exclusion criteria:
  - Case reports, editorials, opinion pieces, and animal studies.
  - Studies with insufficient sample sizes (< 30 subjects) or those lacking statistical rigor (e.g., non-randomized, unvalidated methodologies).
  - Non-peer-reviewed literature, conference abstracts, or unverified preprints.

2.3 | Data Synthesis

Data from the selected studies were synthesized narratively, with an emphasis on:

- The impact of gut-microbiota-brain axis alterations on IBD pathophysiology.
- Psychosocial factors in IBD management.
- Latest therapeutic interventions and mechanisms of action.

This synthesis aimed to provide a multidimensional perspective on IBD treatment, integrating innovative approaches and potential care strategies that address both the physiological and psychological aspects of IBD. To minimize bias, preference was given to randomized controlled trials and high-quality meta-analyses. Conflicting study results were analyzed based on methodological rigor, population size, and consistency with broader literature findings. We acknowledge potential publication bias and the heterogeneity across trials, especially in studies assessing FMT and biologic therapies.

3 | Discussion

3.1 | Pathogenesis of IBD

Inflammatory Bowel Disease is an umbrella term encompassing any chronic inflammatory disorder of the gastrointestinal tract (GIT) [4]. This includes Crohn's disease (CD), ulcerative colitis (UC), and IBD unclassified. The burden of IBD worldwide has risen substantially over the last decade, as recent studies show as much as a 46% and 169% increase in the prevalence and incidence of IBD, respectively, from 2006 to 2021 [5]. Over the last 50 years, IBD has been reported to have spread into the developing world, as well as alarming increases in pediatric-onset incidence rates [6]. Despite being a manageable diagnosis, it is not uncommon for complications to arise; they can be severe and debilitating to the patient, causing them to experience an array of symptoms, including diarrhea, abdominal pain, fever, and weight loss [7]. Moreover, it is essential to consider the financial burden of IBD. As of 2016, the US predicts a $875 billion cost for IBD patients nationwide [8].

Although the pathogenesis of IBD is not well understood, it is well-cited that the persistent GIT inflammation is the result of an inappropriate immune response to an unknown trigger [9]. Furthermore, various reports support the multifactorial theory that suggests that the interaction between genetic predisposition, environmental triggers, and alterations to gut

microbiota leads to IBD. In 1988, a European report found a probable concordance in monozygotic twins of 58.3% and 6.3% in CD and UC, respectively. In contrast, the proband concordance in dizygotic twins was 3.9% in CD, and none were found in UC [10]. This indicates the presence of a significant genetic factor in IBD. Although not exhaustive, extensive research in the genetic predisposition of IBD found 242 common susceptibility loci, with NOD2, TNFSF15, and human leukocyte antigen to be the most significant [10, 11]. The NOD2 gene mutation is the strongest genetic risk locus and is strongly associated with increased *E. coli* in the intestine [12, 13]. NOD2 is an intracellular pattern recognition receptor that identifies muramyl dipeptide, a component of bacterial peptidoglycan, thereby playing a crucial role in the innate immune system's ability to detect and respond to bacterial pathogens. Mutations in NOD2 can impair this recognition, leading to inadequate immune responses and increased susceptibility to intestinal inflammation. Another notable genetic mutation is ATG16L1, a gene that contributes to the lysosomal degradation and clearance of pathogens, better known as the autophagy pathway. Mutations in ATG16L1 can disrupt autophagy, leading to impaired clearance of bacteria and dysfunctional immune responses. This impairment contributes to the persistence of inflammation characteristic of IBD.

The interaction between NOD2 and ATG16L1 is particularly noteworthy. NOD2 can recruit ATG16L1 to the plasma membrane at the bacterial entry site, initiating autophagy in response to bacterial invasion. Mutations in either gene can disrupt this process, leading to defective bacterial handling and increased inflammation [14].

Various studies also indicate the importance of gut microbiota in IBD, even suggesting it may be the primary cause of the disease [14–16]. Gut microbiota plays a crucial physiological role in many homeostatic GIT processes, from facilitating the production of short-chain fatty acids to synthesizing vitamins [17]. Furthermore, gut microbiota directly alters the balance between Treg and Th17 cells, which regulate the pro-inflammatory and anti-inflammatory cytokines in the GIT. Subsequently, this imbalance leads to the pathogenesis of IBD, and this theory has been well-cited [18, 19]. This theory is further supported by the substantial difference in the diversity of the gut environment between a healthy person and an IBD patient [20, 21]. A noteworthy component of the gut is the indigenous macrophages found in the subepithelial layer of the lamina propria (SLP), which protect the intestinal walls from commensal microorganisms' attack. A study demonstrated that 59% of IBD patients had a weakened SLP layer, and 9% had lost theirs completely. In contrast, only 31% of control patients had a weakened SLP, and none completely lost theirs, displaying the importance of the gut environment in deterring intestinal wall inflammation [22].

The study of environmental triggers that lead to IBD is extensive and includes infections, smoking, and diet. The most notable infective trigger is *Mycobacterium avium paratuberculosis*, associated with CD since its original description in 1913 [23]. A study carried out in 2006 by Zhang et al. found a 92% prevalence of *Helicobacter* in pediatric IBD patients, while only 25% in pediatric controls [24]. Moreover, another study yielded a 79% prevalence of non-*pylori Helicobacter* in adult patients with UC, while only 23% in control patients [25]. The intricate relationship between infectious agents and Inflammatory Bowel Disease (IBD) development highlights the complexity of this condition's etiology [25]. *Mycobacterium avium paratuberculosis* (MAP) was one of the first pathogens suggested to play a role in IBD, drawing parallels with Johne's disease in cattle. The debate around MAP's role in IBD, particularly Crohn's disease, is symbolic of the broader discussion on infectious triggers in IBD. This conversation includes other bacterial species, such as non-*pylori Helicobacter* and adherent-invasive *Escherichia coli* (AIEC), associated with IBD pathology. AIEC, for instance, exhibits a specificity to ileal Crohn's disease, suggesting a nuanced interplay between the host's immune response and microbial agents. The potential role of infectious agents extends beyond direct causation, implicating a shift toward dysbiosis and chronic intestinal inflammation. This underscores the importance of considering both the microbiome's composition and its interaction with the host's immune system in understanding and managing IBD [25–28]. Figure 1 shows the host–microbe interactions in IBD pathogenesis.

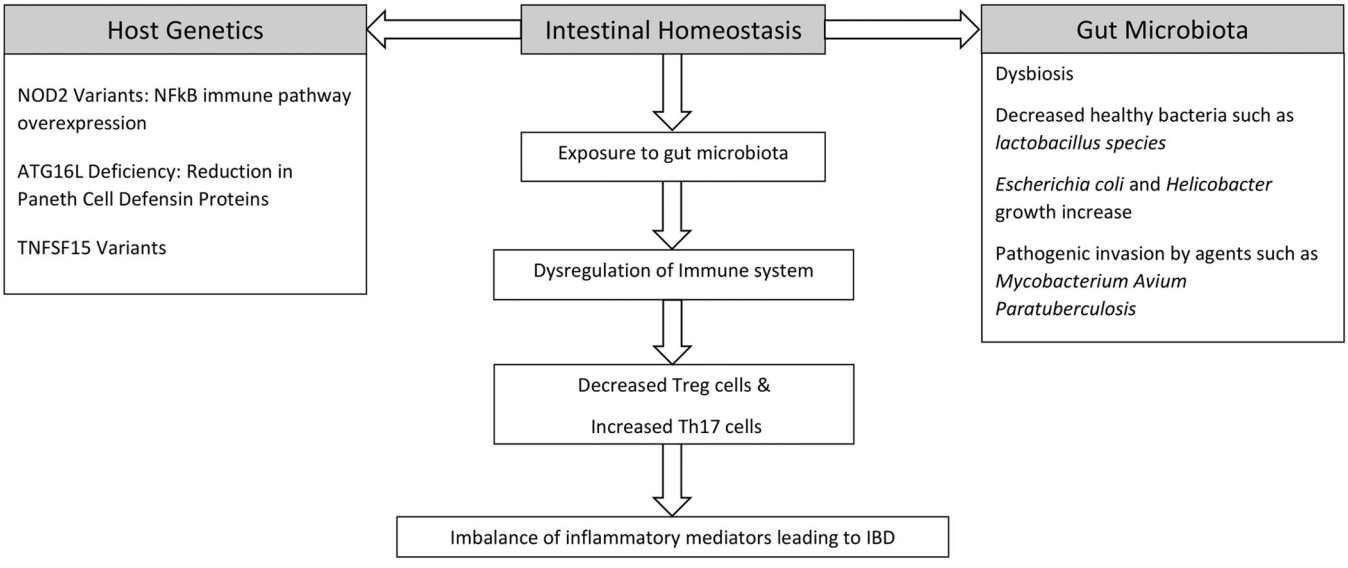

FIGURE 1 | The host–microbe interaction in IBD pathogenesis.

In addition to infections, smoking is another well-documented environmental factor leading to IBD. A meta-analysis conducted by Calkin 1989 compared smokers to non-smokers and demonstrated a pooled odds ratio of 2.0 and 0.41 in CD and UC, respectively [29]. Further research suggests smoking increased the risk of clinical, surgical, and endoscopic recurrence in patients who underwent surgery for CD [30]. In contrast, there are a few papers that suggest smoking reduces the risk of developing UC and that it may even play a role in alleviating symptoms [31, 32]. The mechanism behind the benefits observed in smoking with UC is unclear, but multiple research papers suggest nicotine is the active component responsible for this effect [33]. Smoking plays a paradoxical role in the realm of IBD, offering protection against ulcerative colitis (UC) while exacerbating Crohn's disease (CD) [34]. This dichotomy not only influences the susceptibility to these diseases but also affects their clinical trajectories. For UC patients, smoking appears to delay the onset and mitigate the severity, reducing the necessity for colectomy and potentially ameliorating the disease's course. Conversely, smoking increases the risk of developing CD and aggravates its progression, leading to an elevated requirement for medical interventions, including steroids, immunosuppressants, and surgical operations [35]. The cessation of smoking presents its own set of consequences—worsening UC while beneficially impacting CD. The underlying mechanisms for these opposing effects of smoking on UC and CD remain elusive [36], highlighting the intricate interplay between genetic predispositions, environmental factors, and the immune system in the pathogenesis of IBD. This complex relationship underscores the need for tailored smoking cessation advice for patients, taking into account the specific type of IBD, to avoid inadvertently aggravating their condition [37].

The Swiss IBD Cohort Study, conducted to understand the influence of lifestyle factors on the onset of CD and UC, provides insightful observations into environmental factors contributing to inflammatory bowel disease (IBD) [37]. Engaging 2294 patients, the study employed questionnaires to gather detailed information on patients' physical activities, nutritional habits, and weight status. A unique aspect of this study is that it includes a control group comprised of patients' childhood friends, offering a comparative analysis of environmental exposures. The findings reveal a protective effect of regular physical activity against IBD development, emphasizing the significance of exercise in preventing these conditions. Furthermore, the study observes no direct association between refined sugar intake and IBD onset, challenging the commonly held belief about sugar's role in these diseases. Notably, a higher prevalence of overweight conditions during childhood was explicitly linked to CD, highlighting the impact of early-life weight status on disease risk. Additionally, breastfeeding practices and premature births were explored, revealing nuanced connections to IBD risk, particularly in UC cases. The study underscores the complex interplay of diet, physical activity, and early-life exposures in the pathogenesis of IBD, suggesting avenues for preventive strategies and further research [37].

It is worth noting that diet has also been well-cited as a defining risk factor when it comes to the development of IBD. More specifically, the Westernized diet reduces gut microbiota diversity and subsequently increases the risk of IBD development [38]. In exploring the nuanced relationship between diet, nutrition, and the pathogenesis and management of IBD, including CD and UC, current literature underscores the complexity and individual variability in dietary impacts on IBD. Research indicates a significant, yet not fully understood, role of diet in both the onset and management of IBD, suggesting that environmental factors, in tandem with genetic susceptibility and alterations in gut microbiota, may contribute to the disease's etiopathogenesis through dysregulated immune responses [39]. Protective dietary factors such as breastfeeding, high fiber intake for CD, and omega-3 polyunsaturated fatty acids for UC have been identified, while diets rich in animal fats, cholesterol, and specific sugars are associated with increased IBD risk. Therapeutic diets, including Exclusive Enteral Nutrition (EEN) and the Crohn's Disease Exclusion Diet (CDED) with Partial Enteral Nutrition (PEN), have shown promise in inducing remission, particularly in pediatric cases of CD, albeit with challenges related to dietary adherence and potential nutritional deficiencies [40]. This body of evidence points to the critical need for individualized dietary recommendations in IBD management, tailored to each patient's nutritional requirements and clinical profile. It further highlights the imperative for ongoing research to elucidate the mechanisms by which diet influences IBD pathogenesis and progression, to refine dietary guidelines, and to enhance patient care [41].

3.2 | The Gut–Brain Axis in IBD

In the study on the gut–immune–brain axis and its implications in IBD, a comprehensive analysis is proposed that highlights the intricate interactions between chronic intestinal inflammation, systemic inflammation, neuroinflammation, and their contributions to neuropsychiatric comorbidities, such as depression and anxiety. The study delves into how chronic intestinal inflammation in IBD—which includes Crohn's disease (CD) and ulcerative colitis (UC)—facilitates the breach of the gut barrier, leading to systemic inflammation [42]. This systemic inflammation, in turn, communicates with the central nervous system (CNS) through various pathways, including the vascular system and the enteric nervous system, ultimately leading to neuroinflammation, as illustrated in Figure 2. Specific attention is given to the role of gut microbiota in modulating these interactions. Alterations in the composition of gut microbiota, often seen in IBD patients, are pivotal in the pathogenesis of intestinal inflammation and influence the gut–immune–brain axis, impacting CNS function and behavior [43]. The study highlights how dysbiosis contributes to the exacerbation of IBD and neuropsychiatric symptoms through the production of neuroactive compounds, modulation of the immune response, and direct effects on the CNS. Although not well researched, the gut-brain axis has recently been the topic of various studies that aim to explore therapeutic options that target it [44]. The gut–brain axis is a bidirectional communication network that links the Enteric Nervous system (ENS) and the central nervous system (CNS) [45]. These connection routes are facilitated by enteroendocrine cells connecting to neuropod cells and subsequent synapses with the vagus nerve. Strong evidence suggests that ENS can strongly influence mucosal immunity and thus contribute to the development of IBD [45].

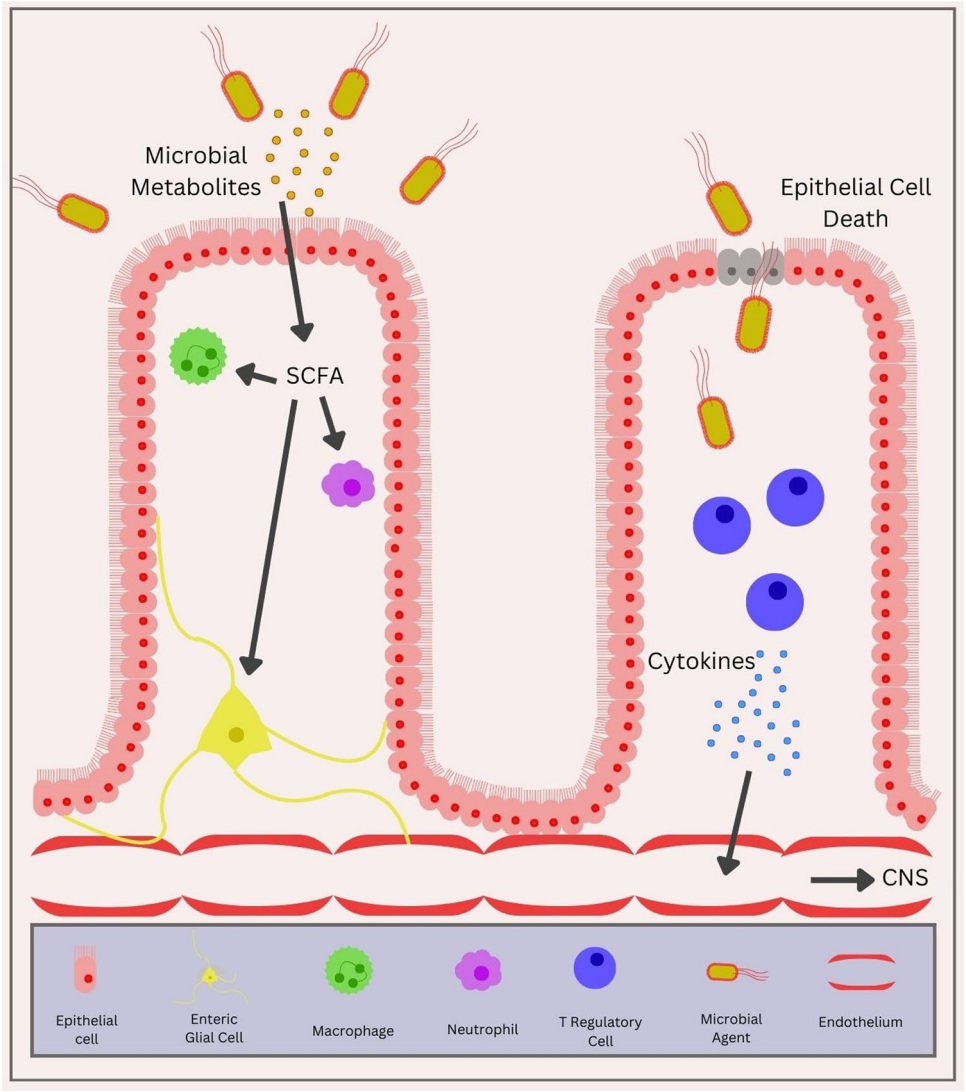

FIGURE 2 | The impact of intestinal inflammation on the gut–brain axis.

The gut can modulate brain function through hormonal, neural, metabolic, and immunological pathways. An example of this is the cytokines released by the mucosal immune cells in response to local inflammation that can reach the CNS via the bloodstream. Additionally, neuroactive bacterial metabolites can influence the gut–brain axis and neuroinflammation.

Furthermore, studies explore therapeutic strategies that target these complex interactions. Probiotics, prebiotics, and diet modifications aimed at restoring gut microbiota balance, as well as interventions directly targeting neuroinflammation, could offer new avenues for alleviating IBD symptoms and its neuropsychiatric comorbidities [46]. The potential of these therapies to improve patient outcomes by addressing the gut–immune–brain axis underscores the importance of an integrated approach to managing IBD. Another study underscores the pivotal role of the microbiota–gut–brain axis in the development of Inflammatory Bowel Disease (IBD) [47], highlighting its profound impact on both local inflammation and neuropsychiatric manifestations in IBD patients. It discusses how the convergence of microbial signals with the host's neuronal, immune, and endocrine systems can modulate disease severity and patient mood, potentially influencing treatment efficacy. Recent findings on the involvement of microbial metabolites, such as bile acids, short-chain fatty acids, and tryptophan metabolites, in IBD pathogenesis and symptomatology at gastrointestinal and central nervous system levels are presented. Furthermore, the study evaluates current microbiome-targeted therapies, including antibiotics, probiotics, prebiotics, and fecal microbiota transplantation, for their ability to address the gastrointestinal aspects of IBD and associated neuropsychiatric conditions [48]. This study emphasizes the intricate interplay within the microbiota-gut-brain axis in shaping the complexity of IBD, advocating for advanced therapeutic approaches to target this multifaceted relationship [48].

Drawing from the comprehensive analysis by Gracie et al., it is evident that the interplay between psychological well-being and gastrointestinal (GI) disorders, particularly in IBD, underscores a complex relationship mediated by the brain-gut axis. The presence of psychological disorders such as anxiety and depression not only exacerbates GI symptomatology but also may predispose individuals to the onset of GI disorders and vice versa [49]. Through epigenetic modifications, the gut

microbiota may be involved in the pathogenesis of certain neuropsychiatric disorders. These epigenetic modifications are highly dynamic and reversible, so if we were to modify the microbes and their metabolic products, it could help us modify the epigenome, thus helping prevent or treat the mental disorder [50]. This bidirectional interaction suggests a pivotal role of the brain–gut axis, potentially offering a therapeutic target. While treatments aimed at rectifying disordered brain–gut interactions, including psychological therapies and antidepressants, show promise in improving symptoms and quality of life in irritable bowel syndrome (IBS), their efficacy in IBD remains uncertain due to the lack of interventional studies [49]. However, as suggested by observational data, the substantial impact of these interactions in IBD highlights the necessity for further research. Well-designed trials focusing on psychological therapies and antidepressants, especially for patients experiencing coexistent psychological disorders or reporting IBS-type symptoms, are imperative. Integrating such treatments within a biopsychosocial model of care could potentially enhance both psychological well-being and quality of life for some patients with IBD, thereby reducing healthcare utilization and possibly altering the disease's natural history [49]. This approach emphasizes the importance of considering the brain–gut axis in the comprehensive management of IBD, advocating for a paradigm shift towards a more holistic understanding and treatment of the disease. Another study by Gravina et al. explores the impact of psychotherapy on therapeutic adherence among IBD patients, including those with Crohn's disease, ulcerative colitis, and indeterminate colitis [51]. The authors highlight a tentative positive effect of psychotherapy, notably cognitive-behavioral therapy, on enhancing therapeutic adherence, albeit acknowledging existing studies' limited scale and definitive nature. Emphasizing the critical role of adherence in the effective management of IBD—a condition characterized by its remitting-relapsing nature and the prevalent psychological and psychiatric comorbidities among sufferers—the review delves into various psychotherapeutic interventions like telemedicine, mindfulness, and hypnotherapy techniques. However, it calls for more rigorous research to substantiate the preliminary findings. The review posits psychotherapy as an adjunct strategy in the comprehensive management of IBD, addressing both the induction of remission and the sustenance of health, thereby spotlighting the intricate psychological dimensions influencing treatment adherence and the broader management spectrum of IBD [51].

Another study by Peppas et al. highlights the complex interrelation between psychological factors and gastrointestinal health, particularly in the context of IBD [52]. It underscores the significance of the gut-brain axis, illustrating how psychological stress exacerbates IBD symptoms through mechanisms like altered gut motility, microbiota composition changes, and increased gut permeability. The research points to probiotics as beneficial for gut health and psychological well-being by modulating stress responses and neurotransmitter production, suggesting their dual role in managing IBD and associated depressive symptoms. Additionally, the study explores dietary interventions, specifically the low FODMAP diet, in improving gastrointestinal symptoms and, by extension, psychological stress and overall quality of life for IBD patients. Fecal Microbiota Transplantation (FMT) is also discussed as a promising treatment with potential psychological benefits due to its role in restoring a healthy gut microbiota balance, which indirectly affects mental health. This comprehensive view highlights the need for a holistic approach to treating IBD, addressing both the physical and psychological aspects to improve patient outcomes [52].

A recent study by Massironi et al. reinforces the association between IBD and psychiatric comorbidities, identifying depression and anxiety as prevalent concerns. The findings emphasize the need to consider the gut-brain axis in comprehensive IBD care and support the therapeutic relevance of psychobiotics and neuroinflammation-targeted strategies [53].

According to Tsange Tse et al., it is clear that the dynamic and bidirectional interplay between the gut and brain is pivotal not only in the pathophysiology of IBD but also in the manifestation of neurobiological symptoms such as anxiety, depression, fatigue, stress, and sleep disturbances [54]. These symptoms significantly affect patients' quality of life and functional abilities, underscoring the urgency for clinical trials focused on pharmacological and nonpharmacological interventions. This approach aligns with the latest regulatory guidelines and seeks to place patients' experiences at the core of medical and regulatory decision-making, potentially revolutionizing patient care by integrating patient-centered care and shared decision-making into the treatment paradigm for IBD, thereby making a significant impact on the management of the disease and enhancing patients' overall well-being [54].

Günther et al. [41] highlight in their review that the gastrointestinal tract, hosting over 100 trillion microbial cells, significantly impacts intestinal and extraintestinal diseases. Clinical studies have revealed a common pattern of reduced diversity and altered composition in the gut microbiota, known as dysbiosis, in neuroinflammatory and neurodegenerative conditions, such as Parkinson's Disease (PD) and Multiple Sclerosis (MS). While the precise role of dysbiosis in disease progression remains under debate, evidence suggests a causative link between gut microbes and CNS disorders. For instance, germ-free mice resisted experimental autoimmune encephalomyelitis (EAE), indicating the essential role of gut microbes in initiating neuroinflammatory responses. Further, fecal microbiota from PD patients worsened symptoms in a PD mouse model, underlining the influence of gut microbiota on neurodegeneration. This relationship is thought to be mediated by microbial metabolites affecting the gut barrier and inflammatory processes, contributing to pathological conditions like PD. The study also explores how dietary tryptophan metabolites produced by the microbiota can limit CNS inflammation by affecting microglia and astrocytes. Additionally, it points out that the gut microbiota can alter drug bioavailability and efficacy, exemplified by the variable response to Levodopa in PD treatment based on individual microbiota composition. This study underscores the profound impact of the gut–brain axis on neuroinflammation and neurodegeneration, offering insights into future therapeutic strategies targeting the microbiota to treat CNS disorders [41].

3.3 | Current Treatment Options for IBD

According to the WGO Practice Guidelines, there are various drug and surgery treatment options for IBD patients, each with a

role in a specific phase of pathology. More so for UC than CD, aminosalicylates have been proven to be effective in both inducing remission and a role in maintenance. A notable biological drug is anti-TNF agents, an example being Infliximab, that have demonstrated effectiveness in severe perianal CD and rescue therapy in corticosteroid-refractory severe UC. Vedolizumab, another biological agent, demonstrates effectiveness in inducing and maintaining remission. In more extreme cases, corticosteroids can suppress inflammation and rapidly relieve symptoms. Antibiotics and probiotics also play a role in treating CD and UC complications. The most used class of drugs is immunomodulators, which consist of thiopurines and methotrexate, both of which are ineffective at inducing remission but are proven to be effective at maintenance. Immunomodulators reduce or eliminate corticosteroid dependence and are the primary choice if aminosalicylates and corticosteroids are ineffective long-term. Calcineurin Inhibitors, another immunomodulator drug, are reserved for acute severe colitis. A range of surgeries are also used in cases of refractory disease, and they can be very effective in inducing long-term remission. In CD, ileocecal resection is the primary option, as well as many other surgeries used to correct complications, like drainage of abscesses, bowel-sparing stricturoplasty, and ileorectal or ileocolonic anastomosis. In UC, total proctocolectomy plus permanent ileostomy proved an effective treatment for inducing long-term remission [29]. A summary comparison of the efficacy and mechanisms of different immunomodulatory therapies and their impact on the gut–brain axis is represented below in Table 1.

TABLE 1 | Comparative summary of immunomodulatory therapies in IBD and their impact on the gut–brain axis.

Therapy	Mechanism of action	Gut–brain axis impact	Reported efficacy	Limitations
Fecal microbiota transplant (FMT)	Restores microbial diversity	Modulates neuroactive metabolites	Up to 87% remission	Donor variability; safety concerns
Infliximab (anti-TNF)	Neutralizes TNF-alpha	Reduces systemic inflammation affecting the CNS	40%–69% remission	Infection risk; immunogenicity
Stem cell therapy	Immune modulation and tissue repair	Restores epithelial integrity and immune balance	Promising in pilot studies	High cost; regulatory hurdles
Probiotics	Competitive inhibition of pathogens; anti-inflammatory	Reduces gut inflammation; modulates stress pathways	Adjunct symptom relief	Inconsistent efficacy; species-specific effects

3.4 | Recent Advancements in Immunomodulatory Therapies Targeting the Gut–Brain Axis

- Fecal microbiota transplant

  Fecal Microbiota Transplant (FMT) was first introduced in 1958 by Eiseman and colleagues. They proved that using fecal enemas was an effective treatment for Pseudomembranous colitis [55]. FMT involves administering a minimally manipulated microbial community from stool from a healthy donor into the patient's intestines through various routes, including nasogastric tube, oral capsule, and retention enema [51, 56]. In contrast to other therapeutic alternatives, FMT functions to provide a functional ecosystem comprising the full spectrum of microbial organisms that inhabit a healthy intestine, which has the potential to correct dysbiosis, which is a critical factor in IBD development [57]—Nigam et al. highlight significant progress in FMT as an emerging immunomodulatory therapy. FMT is gaining traction as a pivotal strategy for re-establishing a healthy gut microbiota balance, which is instrumental in metabolism, immune defense, and warding off pathogens. This procedure has shown promising results in treating a range of disorders, from gastrointestinal diseases like IBD and recurrent Clostridium difficile infections to extraintestinal conditions, including obesity, metabolic syndrome, and even neurological disorders. Recent advancements underscore FMT's potential to modulate the immune system by altering the gut microbiome's composition, offering a novel approach to treating diseases with underlying immune dysregulation. The article emphasizes the need for

further research into FMT's mechanisms of action, long-term effects, and integration into broader immunomodulatory therapy frameworks, pointing towards a future where FMT could become a standardized treatment option within immunotherapy portfolios [58].

In general, FMT is a relatively safe procedure associated with minimal adverse effects. Short-term adverse effects include transient diarrhea, bloating, abdominal cramps, and fever, most of which are related to the method of delivery [59]. Although they are rare, it is vital to consider the long-term effects of FMT. The long-term implications of FMT are majorly unknown due to the infrequent intervals at which the procedure was administered to patients. The population in which this therapy was conducted mostly pertained to university-based hospitals, and this geographic discrepancy brings further doubt to the prolonged efficacy of the therapy in various gastrointestinal diseases. In patients with ongoing symptoms of diarrhea and post-antibiotic dysbiosis, probiotics helped alleviate the symptoms better than FMT [60]. There were reports of two cases of extended-spectrum beta-lactamase-producing *E. coli* and six cases of Shiga toxin-producing *E. coli* transmitted to the host via FMT, three of which caused subsequent deaths. Following this, the FDA mandated additional drug-resistant screening in stool banks [61]. In a few cases, long-term adverse effects were observed, and the patient's susceptibility to various diseases increased. Obesity, rheumatoid arthritis, and thrombocytopenia are among the diseases associated with FMT [62]. Furthermore, a few cases report FMT inducing ulcerative colitis and IBS 6 months post-FMT [63].

Despite the high remission rates reported in select studies, response to FMT in IBD remains highly variable. Differences in donor microbiota composition can significantly impact therapeutic efficacy, highlighting the need for standardized donor screening and preparation protocols. Furthermore, long-term safety remains uncertain. Reports of post-FMT onset of IBS, Ulcerative Colitis, and even transmission of pathogenic bacteria (e.g., extended-spectrum beta-lactamase-producing *E. coli*) underscore the need for caution and rigorous follow-up.

- Biologic therapies and stem cell therapy

The interaction between new therapies, particularly immunomodulators, and the gut–brain axis presents a compelling frontier in the treatment of IBD, such as UC and CD. The gut–brain axis is the bidirectional communication pathway between the gastrointestinal tract and the central nervous system, encompassing immune, hormonal, and neuronal signals. Recent studies and advances in biological and stem cell therapies have underscored the potential of targeting this complex interaction to manage IBD more effectively [64]. Biologic therapies, such as monoclonal antibodies against tumor necrosis factor (TNF) alpha (e.g., Infliximab) and integrin receptor antagonists, offer targeted immunomodulation [65]. These agents can directly influence the inflammatory pathways implicated in IBD, potentially reducing the disease's impact on the gut–brain axis. By mitigating gut inflammation, these therapies may alleviate central nervous system symptoms like anxiety and depression, which are more prevalent in IBD patients [66]. Stem cell therapy represents a novel approach with the potential to modulate the immune response and contribute to the regeneration of damaged intestinal tissue [64]. This can have profound implications for restoring the integrity of the gut–brain axis, improving both gastrointestinal and neurological outcomes for patients.

Mishra et al. discuss the potential of stem cell therapy as a groundbreaking treatment for IBD, including both ulcerative colitis and Crohn's disease [64]. These conditions are debilitating autoimmune disorders that not only affect patients' quality of life but also increase the risk of colitis-associated cancer. Given the chronic nature of IBD and the limitations of current treatments, which have inconsistent outcomes and severe side effects, there is a significant interest in alternative therapies. Stem cell therapy, utilizing either hematopoietic or mesenchymal stem cells, offers a promising avenue due to their pluripotent nature and ability to differentiate into epithelial and/or immune-modulatory cells. This innovative approach aims to facilitate mucosal healing by migrating to damaged areas of the intestine, thus potentially restoring barrier integrity and preventing the immunomodulatory induction at the root of IBD [64].

Biondi et al. discuss the challenges faced by patients and healthcare providers due to the unpredictable nature of UC, a chronic inflammatory condition affecting the colon and rectum, which often leads to severe symptoms and complications [67]. Despite the introduction of biologic therapies, such as Infliximab, which target specific aspects of the immune response, a significant proportion of UC patients eventually require surgical intervention due to the failure of medical therapy, the onset of severe complications, or the development of malignancy associated with long-term inflammation. The traditional surgical option of colectomy can offer a definitive cure by removing the source of inflammation, but it also significantly affects patients' lifestyles. The evolution of surgical techniques, particularly the adoption of Restorative Proctocolectomy with Ileal Pouch-Anal Anastomosis (IPAA), is presented as a gold standard that preserves the anus and avoids a permanent stoma, improving patients' quality of life [68]. However, the decision for surgery, especially in the era of biologic therapies, is complex and involves assessing the risks of ongoing medical therapy against the potential complications and lifestyle changes associated with surgery. The impact of preoperative biologic therapy on surgical outcomes, noting that patients on these medications might face increased risks during and after surgery, including infection and complications related to wound healing. It suggests that despite the benefits of biological therapies in managing UC, their role in altering the long-term need for surgical intervention remains uncertain, and they may only delay rather than prevent the need for surgery in specific patient groups.

One of the significant challenges with new therapies, including biologics, is the variable patient response [69]. A substantial proportion of patients either do not respond to these treatments or lose response over time, necessitating

surgical intervention or alternative therapies. This variability can complicate the management of IBD and its effects on the gut–brain axis. Patients undergoing biologic therapy, especially those on TNF alpha inhibitors, may face increased risks during and after surgical procedures. These risks include infections and complications related to wound healing. The interaction between these drugs and surgery can complicate decisions regarding the timing and type of surgical intervention for IBD [70]. Furthermore, the long-term safety and efficacy of new therapies, mainly stem cell treatments, remain areas of active investigation. Questions remain regarding the potential long-term impacts on the gut–brain axis, including whether these therapies can sustainably restore gut function and mitigate neurological symptoms associated with IBD.

IL-23 is pivotal for the development of IBD. One way to treat IBD is by neutralizing IL-23. Anti-IL-23 agents are used in patients for a more precise reduction in inflammation than broad-spectrum immunosuppressants. The drug Ustekinumab has been effective in inducing and maintaining remission in patients with CD and has worked on patients for whom no other biological agent has worked. JAK inhibitors like Izencitinib also block IL-23 via the JAK-2 and STAT3 pathways. The dangerous complications like hepatotoxicity, drug-induced skin lesions, tuberculosis, and lymphoma caused by anti-IL-23 agents cannot be neglected, and thus, the need for therapies with another mechanism of action that maximizes treatment efficacy with minimal side effects is necessary [71, 72]. JAK inhibitors are preferred over other biologics since they are administered orally instead of subcutaneous or intravenous routes like the other agents. They are also better than monoclonal antibodies, which block only a single cytokine. JAK inhibitors affect multiple cytokine-dependent immune pathways, which may improve the therapeutic response of some patients with IBD [72].

New therapies, especially biologics and stem cell treatments, are often expensive and may not be accessible to all patients [73, 74]. This limitation can impact the equitable management of IBD and its effects on the gut–brain axis across different patient populations. The interaction of new therapies with the gut–brain axis in the context of IBD treatment presents exciting opportunities and significant challenges. While targeted immunomodulation and the therapeutic potential of these treatments offer new hope for patients, variability in response, impacts on surgical outcomes, questions regarding long-term safety, and issues of cost and accessibility must be carefully navigated. Future research to understand and optimize these interactions will be critical in improving the care and quality of life for patients with IBD.

- Probiotics

  Probiotics have been proven to be a protective measure against inflammatory bowel diseases through various modes of action. Introducing probiotics like Lactobacilli and Bifidobacteria helps stabilize the intestinal ecosystem by competing for nutrients, which inhibits the development of harmful pathogens like *E. coli*, *C. difficile*, and *Pseudomonas* [75]. Moreover, probiotics have been proven to increase local mucin production, which acts as an adhesion medium to prevent pathogenic adhesion to intestinal walls. However, the most important mechanism of action is their anti-inflammatory effect on the intestinal walls [76]. Several studies demonstrated that probiotics reduce inflammation and the immune response by correcting the imbalance between pro- and anti-inflammatory cytokines, Treg, and Th17 cells. Furthermore, probiotics also reduce the overall pro-inflammatory cytokines levels, like TNF-alpha and IFN-g, both systemically and locally [77].

  Probiotics have also been reported to alleviate many of the complications of IBD. This is accomplished by probiotics targeting the gut–brain axis. Several studies report the benefit of *B. lactis* HN019 against constipation and gut dysmotility [78]. This is achieved via the short-chain fatty acids produced during bacterial fermentation that alter the serotonin signaling pathway, resulting in increased transit time in constipation. Another symptom of IBD that can be alleviated with probiotics is visceral hypersensitivity [79]. The bacterial metabolites produced by probiotics act as neurotransmitters that apply direct antinociceptive effects on the intestinal wall by targeting the gut-sensitive nerve endings. Furthermore, Suggestions are made that probiotics may have a role in antinociceptive and nociceptive balancing even at a CNS level through the gut–brain axis. This is further established by the protective effect that probiotics have been proven to have against stress-induced anxiety and depressive disorders [80]. These are called psychobiotics and are live bacteria that interact with the gut–brain axis to confer mental health benefits [81].

  It is important to note that although probiotics have been proven to alleviate many IBD-associated symptoms, they do not induce remission, nor have they proven to be an independent, effective maintenance treatment option. The advantage of probiotic use is the lack of adverse effects compared to other therapeutic alternatives. However, in some studies, the use of some probiotic species like *Lactobacillus paracasei* species, Paracasei F19, and *L. acidophilus* La5 has seemed to have a detrimental effect on the disease. In a study done at Crohn's and Colitis ulcerosa Vereniging Nederland, it was observed that women responded better to the intake of probiotics than their male counterparts [82, 83]. A systematic review comparing IBD patients who were administered probiotics and those administered placebos concluded that the only side effect of significance between the two groups is abdominal pain, with a related heterogeneity of 40% and an AR of 0.085 [84].

- Implementation strategy

  The clinical implementation of advanced therapies like stem cell treatment and FMT is hampered by several challenges. These include high costs, often not covered by insurance, and limited availability at specialized centers. Moreover, regulatory constraints such as the FDA's evolving stance on FMT and stringent guidelines for stem cell usage further complicate their routine clinical use. Addressing these barriers is essential for broader adoption.

4 | Conclusion

There are several therapeutic options for IBD, including agents that induce remission, such as aminosalicylates, corticosteroids,

and biologics, and those that maintain remission, like immunomodulators. Despite the role of surgery in refractory cases, pharmacological interventions remain central due to the high risk of recurrence. Recent advancements have introduced gut–brain axis-targeted therapies, including stem cell treatments, biologics like anti-TNF agents and integrin antagonists, probiotics, and FMT, all aiming to modulate immune responses and restore gut microbiota balance. However, the clinical implementation of these therapies remains limited by variability in patient response, accessibility, and long-term safety concerns. Future research should prioritize identifying predictive biomarkers for therapy selection, understanding neuroinflammatory mechanisms in IBD, standardizing FMT protocols, and addressing cost and access barriers. Additionally, incorporating neuropsychological interventions such as psychobiotics and cognitive-behavioral therapy may enhance outcomes by addressing the bidirectional gut–brain axis. These approaches represent promising, yet still evolving, avenues in the comprehensive management of IBD.

Author Contributions

Mayank Jha: conceptualization, methodology, investigation, writing – original draft, and supervision. **Aiman Waheed:** validation, formal analysis, and data curation. **Jubran Al Hooti:** conceptualization, methodology, writing – original draft, and supervision. **Shreya Nair:** conceptualization, and writing – original draft. **Ali Najam:** writing – original draft, writing – review and editing, and conceptualization. **Madho Mal:** investigation, writing – review and editing, methodology. **Nayanika Tummala:** methodology, writing – original draft, and investigation. **Abdul Sattar Shariq:** writing – review and editing, validation, and methodology. **Abu Hurairah:** methodology, validation, writing – review and editing. **Michael Daniel:** writing – review and editing, methodology, and conceptualization.

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All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

Transparency Statement

All the authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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