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TITLE PAGE

Title: The Role of the Gut-Brain Axis in Inflammatory Bowel Disease and its Therapeutic Implications.

Short running head: The Gut-Brain Axis: A Target for Therapeutic Intervention in IBD

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Abbreviations:

CBT	cognitive behavioural therapy
CD	Crohn's disease
CNS	central nervous system
DGBI	disorder of gut-brain interaction
FC	faecal calprotectin
FMT	faecal microbiota transplantation
FODMAP	fermentable oligosaccharides, disaccharides, monosaccharides, and polyols
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
RCT	randomised controlled trial
TNF	tumour necrosis factor

UC	ulcerative colitis

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SUMMARY

Background: Treatments targeting the gut-brain axis (GBA) are effective at reducing symptom burden in irritable bowel syndrome (IBS). The prevalence of common mental disorders and IBS-type symptom reporting is significantly higher in inflammatory bowel disease (IBD) than would be expected, suggesting potential GBA effects in this setting. Manipulation of the GBA may offer novel treatment strategies in selected patients with IBD.

Aims: To present a narrative review of the bi-directional effects of the GBA in IBD and explore the potential for GBA-targeted therapies in this setting.

Methods: We searched MEDLINE, EMBASE, EMBASE Classic, PsychINFO, and the Cochrane central register of controlled trials for relevant articles published to March 2024.

Results: The bi-directional relationship between psychological wellbeing and adverse longitudinal disease activity outcomes, and the high prevalence of IBS-type symptom reporting highlights the presence of GBA-mediated effects in IBD. Treatments targeting gut-brain interactions including brain-gut behavioural treatments, neuromodulators, and dietary interventions appear to be useful adjunctive treatments in a subset of patients.

Conclusions: Psychological morbidity is prevalent in patients with IBD. The relationship between longitudinal disease activity outcomes, IBS-type symptom reporting, and poor psychological health is mediated via the GBA. Proactive management of psychological health should be integrated into routine care. Further clinical trials of GBA-targeted therapies, conducted in selected groups of patients with co-existent common mental disorders, or those who report IBS-type symptoms, are required to inform effective integrated models of care in the future.

Keywords: Inflammatory bowel disease

Irritable bowel syndrome

Psychological wellbeing

Neuromodulators

Gut-brain neuromodulators

Brain-gut behavioural treatments

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), collectively termed inflammatory bowel disease (IBD), are chronic immune mediated disorders of the gastrointestinal tract, with an estimated prevalence of 6.8 million cases worldwide.[1] The natural history of IBD is one of quiescence interspersed with periods of disease activity, the latter being associated with a myriad of distressing symptoms, including abdominal pain, urgency, rectal bleeding, and diarrhoea. The exact pathogenesis of IBD is unclear but is a presumed consequence of enteric immune system dysregulation in response to alterations in the gut microbiome, triggered by predisposing genetic and environmental factors.[2] Complications of untreated IBD include stricture and fistula formation, venous thromboembolism, malignancy, hospitalisation, and the need for intestinal resection. Preventing such complications requires a proactive treat-to-target approach, with early recognition of persistent mucosal inflammation, and timely escalation of medical therapy.[3]

Clinical remission has traditionally been considered the gold standard therapeutic target in IBD, with patient-reported symptoms assumed to represent mucosal inflammation.[4] However, randomised controlled trials (RCTs) measuring clinical response or remission consistently report high placebo response rates, which fall considerably when objective assessments of disease activity, such as endoscopic evaluation, are adopted.[5-7] Observational studies demonstrate a similar discordance between disease activity indices and biochemical or endoscopic disease activity, suggesting that these clinical disease activity tools overestimate disease activity when used in isolation.[8, 9] Despite endoscopically confirmed disease quiescence, up to half of patients with IBD continue to experience abdominal pain, and one quarter report symptoms which meet the diagnostic criteria for irritable bowel syndrome (IBS),[8-12] a common disorder of gut-brain interaction (DGBI), heavily influenced

by psychological health and typically characterised by the absence of mucosal inflammation.[13-16]

Psychological co-comorbidity is consistently associated with the reporting of IBS-type symptoms in IBD.[10, 11] Furthermore, symptoms of a common mental disorder, including anxiety and depression, are twice as prevalent in IBD than the general population, and increase further during disease flares.[17] Likewise, brain-gut mediated effects have also been identified in IBD, with the presence of a common mental disorder independently associated with increased healthcare utilisation,[10, 18-21] adverse disease outcomes,[8, 22, 23] and anti-tumour necrosis factor alpha (TNFα) discontinuation.[24] Such observations highlight that a cause-and-effect relationship between disease activity and symptom burden in IBD is oversimplistic, and suggest that gut-brain interactions may also be implicated in the generation of symptoms in IBD, mediated via the neurohormonal pathways collectively termed the gut-brain axis (GBA).[10, 25] This complex bi-directional communication system links the central nervous system (CNS) with the gastrointestinal tract, enabling central control of peripheral gut functions.[25] GBA dysregulation is considered key in the pathophysiology of IBS,[14] with many of its treatments centred upon modulation of this network, and with proven efficacy.[26, 27] It is less clear, however, whether targeting the GBA with similar interventions is efficacious in IBD.

This review will consider how gut-brain interactions may influence disease activity, symptom reporting, and psychological wellbeing in patients with IBD. A review of the neurohormonal pathways making up the GBA will be described, and treatment options for the management of IBS-type symptoms and co-existent common mental disorders in IBD discussed.

SEARCH STRATEGY AND SELECTION CRITERIA

We searched MEDLINE, EMBASE, EMBASE Classic, PsychINFO, and the Cochrane central register of controlled trials using the terms “inflammatory bowel disease”, “ulcerative colitis”, “Crohn$ disease”, “irritable bowel syndrome”, combined with the set operator AND with the terms “pathophysiology”, “microbiome”, “mood”, “anxiety” and “depression” for all English language publications up until March 2024. Abstracts were then reviewed to identify publications relevant to the role of the GBA in IBD, and those examining the prevalence, and significance of psychological co-morbidity and IBS-type symptom reporting in patients with IBD. Our search returned >4800 publications, and articles considered by the assessors to be the most substantial contributions to the field were included in this review.

THE GUT-BRAIN-MICROBIOTA AXIS IN IBD

The GBA is a bi-directional communication system encompassing the CNS, autonomic nervous system, enteric nervous system, and hypothalamic-pituitary-adrenal axis, which modulates peripheral gut functions via a series of neural, endocrine, immune, and humoral signals. The GBA is influenced by the gut microbiome, which consists of a network of more than 100 trillion prokaryotic cells. Functions of the microbiome are vast but, under normal physiological conditions, include protecting intestinal mucosal integrity by acting as a first line of defence against pathogenic microbes, and the production of short chain fatty acids, including acetate and butyrate, which serve anti-inflammatory roles.[28] Alterations in microbiome composition and subsequent translocation of inflammatory factors across both the gut-epithelial and blood-brain barrier are recognised to contribute to functional alterations in the CNS and have been implicated in the development of common mental disorders,[29] and

neurological disease, including multiple sclerosis, Parkinson's disease, and Alzheimer's dementia.[30] Altered microbial diversity is also implicated in the pathogenesis of IBD, with reduced bacterial diversity observed in patients with both CD and UC,[2] and further differences identified between individuals with quiescent and active disease, the latter having lower abundances of typical gut microflora.[31] The GBA is also implicated in the aetiology of IBS,[14] where bi-directional gut-brain interactions have been described.[32, 33] These same bi-directional effects in IBD may explain not only the high prevalence of common mental disorders in this cohort of patients, but also the negative impact of low mood on symptom reporting and disease outcomes.

The Gut-brain axis in IBD

In murine models of colitis, direct hypothalamic stimulation, and ensuing release of corticotropin-releasing factor and adrenocorticotropic hormone, induce mast cell degranulation and cytokine secretion, which in turn result in increased intestinal permeability and barrier dysfunction.[34] Stress-related activation of the sympathetic nervous system stimulates catecholamine release in the adrenal medulla, which in turn leads to macrophage activation through nuclear factor kB signalling pathways.[35] The vagus nerve, which inhibits pro-inflammatory cytokines, is downregulated during the acute stress response.[36] Most of the evidence pertaining to brain-gut mediated effects outside of animal models is based on observational research, but perceived stress has been demonstrated to increase the number of circulating pro-inflammatory cytokines in quiescent IBD,[19, 37] and is associated with subsequent disease flares, which would support the findings of murine studies.[9, 38]

The proposed mechanism by which the GBA adversely impacts psychological health is through release of pro-inflammatory cytokines including interleukin-1β, interleukin-6, and

TNFα, which enter the systemic circulation and cross the blood brain barrier, whilst simultaneously activating the enteric nervous system, and vagus nerve afferents. Together these humoral and neural pathways activate the hypothalamic-pituitary-adrenal axis causing an upregulation in production of glucocorticoids which serve anti-inflammatory roles, but are also implicated in the pathogenesis of depression.[25] A summary of the proposed bi-directional effects of the GBA in IBD is provided in Figure 1.

MOOD AND THE BRAIN-GUT AXIS IN IBD

Epidemiology of psychological co-morbidity in IBD

It is estimated that 5% of the global population experience depression during their lifetime, and a further 4% anxiety.[39] For patients with IBD the prevalence is significantly higher, with data from large a systematic review and meta-analysis of over 30,000 patients estimating the pooled prevalence of symptoms of depression and anxiety to be 25% and 32%, respectively.[17] Factors independently associated with psychological co-morbidity in IBD appear to be an aggressive disease phenotype, CD, and female sex.[8, 18] In addition, during periods of disease activity the prevalence of these symptoms increases further, with over half of patients experiencing anxiety and more than a third experiencing depression, suggesting that disease activity could influence the development of these symptoms directly.[10, 17]

Most studies examining psychological health in IBD have been conducted amongst patients with established disease. Thus, determining a cause-and-effect relationship between antecedent adverse psychological health and incident IBD is difficult. However, a recently published multicentre observational study of 155 patients newly diagnosed with IBD also reported over one third of patients suffered with anxiety symptoms, and over 15% depressive

symptoms at the onset of disease.[12] Psychological stress has also been implicated in the development of IBD,[40] and may explain the high levels of reporting of stressful life events by patients in inception cohorts.[12] In keeping with observational study findings, a recent population based cohort study including over 22,000 patients with IBD and 100,000 matched controls, highlighted the comparably high prevalence of both anxiety and depression in IBD, but found the risk of developing symptoms of a common mental disorder develops up to 5 years before the diagnosis of IBD.[40] A meta-analysis examining the temporal effects of depression on incident IBD in over 9 million patients supports these findings, indicating a 17% risk of incident CD and a 23% risk of UC, and suggesting that GBA-mediated interactions may be implicated in the pathogenesis of IBD.[41]

Brain-gut interactions: Describing the impact of psychological co-morbidity on disease outcomes in IBD

Studies examining the association between common mental disorders and adverse disease outcomes in patients with quiescent IBD demonstrate that individuals exhibiting symptoms of a common mental disorder are more likely to experience a flare of disease activity, require escalation of medical treatment, or hospitalisation secondary to uncontrolled IBD activity.[23, 42-44] Symptoms of anxiety appear to exert the greatest effect.[10, 17] In a meta-analysis examining GBA effects in IBD, symptoms of both anxiety and depression were associated with a subsequent increased likelihood of flare, escalation of medical therapy, or hospitalisation.[10] Depressive symptoms at baseline were also associated with an increased risk of IBD-related surgery. Many of the studies included in this meta-analysis did not recruit patients solely in remission, but subgroup analyses of studies reporting outcomes in patients in clinical remission identified a consistent increase in the subsequent likelihood of flare in

patients with anxiety. [18] Common mental disorders are also associated with attenuated response to medical therapies, including anti-TNFα, both due to non-adherence,[24] and primary non-response.[45] In conjunction with adverse disease outcomes, increased healthcare utilisation is observed consistently in patients exhibiting symptoms of a common mental disorder.[8, 18, 23, 46] The presence of common mental disorders is associated with a two-fold increase in the estimated annual healthcare costs of patients with IBD, highlighting a financial incentive to the appropriate management of psychological co-morbidity in IBD, independent of any potential beneficial effect on longitudinal disease activity outcomes.[21]

A potential limitation of existing research is the assessment of mood at a single point in time. Addressing this, a recent study examined mood trajectories over a 12-month period.[18] Anxiety and depression scores were recorded at 3-monthly intervals in 771 patients with IBD. Only 10% of patients with abnormal anxiety or depression scores at baseline improved during subsequent follow-up. This suggests that a single assessment of mood is likely to remain durable over time and may be sufficient for longitudinal studies examining brain-gut interactions in IBD. Another significant limitation of most existing observational studies examining the impact of common mental disorders on disease outcomes in IBD arises from their measure of disease activity. A discrepancy between patient-reported symptoms and objective measures of disease has been alluded to previously, with the former overestimating disease activity.[8, 9] This is supported by a *post hoc* analysis of the multicentre SONIC RCT, comparing the efficacy of infliximab or azathioprine monotherapy versus combination therapy with infliximab and azathioprine for the treatment of CD.[7] A disconnect between symptom reporting and objective evidence of disease activity was noted, with one fifth of patients reporting persistent gastrointestinal symptoms despite endoscopic disease remission. Given that observational studies highlight poor psychological health as an association with persistent symptom reporting in quiescent disease,[8] it is possible that adverse disease

outcomes may reflect the influence of psychological health on behaviour rather than a genuine association with persistent disease activity.

Few studies have applied objective assessments of disease activity in patients with symptoms of a common mental disorder and the results are conflicting. Fairbrass *et al.* reported, in a group of 218 patients in biochemical remission according to faecal calprotectin (FC) levels, that adverse psychological health appeared to increase the risk of subsequent flare and escalation of medical therapy, suggesting genuine brain-gut mediated effects in IBD.[23, 43] Conversely Mules *et al.* found no association between symptoms of a common mental disorder at baseline and subsequent disease activity, also utilising FC as a biochemical marker in a sample of 52 patients.[47] However, this study did identify that gastrointestinal symptoms were strongly associated with the presence of psychological co-morbidity.

Gut-brain interactions: Describing the impact of disease activity on psychological health in IBD

In murine studies, researchers have demonstrated that chemically-induced colitis elicits depression- and anxiety-like behaviour.[48, 49] For mice with such symptoms, an increased expression of inflammatory cytokines, and alteration of mitochondrial function in the hippocampus, has been suggested at autopsy, providing experimental evidence of gut-to-brain effects in murine models of colitis.[49] A meta-analysis of studies reporting the prevalence of common mental disorders in IBD has suggested that over half of patients with active disease have symptoms of a common mental disorder, which is almost 20% higher than the prevalence of these symptoms in patients with quiescent disease.[17] The amount of clinical research examining gut-brain effects in IBD is smaller than brain-gut effects. However, studies largely demonstrate an association between baseline disease activity and

subsequent development of a common mental disorder,[50, 51] and increased health-related anxiety.[52] A meta-analysis examining the bi-directional effects of the GBA in IBD, demonstrated that for patients with IBD and normal anxiety and depression scores, clinical disease activity predicts future development of these symptoms, particularly for anxiety.[10]

GASTROINTESTINAL SYMPTOM REPORTING IN QUIESCENT IBD

Until recently, guidelines have suggested that clinical remission should be the focus of IBD care.[4] This proactive, treat-to-target approach is certainly beneficial when gastrointestinal symptoms correlate with underlying disease activity. However, even when deep remission of IBD is achieved, studies suggest that almost 30% of individuals who fulfil the Rome III criteria for IBS are misclassified by disease activity indices as having active disease.[53] Aside from the obvious financial and resource burden associated with the unnecessary use of immunosuppressive treatments, administration of conventional IBD therapies is ineffective in treating these symptoms,[54-56] and has the potential to cause harm, including opportunistic infection and treatment associated malignancies.[57] Alternative management strategies are therefore required.

Prevalence of IBS-type symptom reporting in patients with IBD

The use of varying definitions of disease quiescence in IBD makes determining the exact prevalence of IBS-type symptoms in this group of patients challenging. Studies conducted in patients with endoscopic remission report a prevalence as low as 11%,[58] and those using subjective measures to define remission as high as 63%.[59] A recent meta-analysis including over 3000 patients reported the overall prevalence of IBS-type symptoms to be closer to one-third of patients, with a higher prevalence amongst patients with CD (36%) than

UC (28%).[11] When patients with objectively confirmed disease quiescence, such as biochemical, endoscopic, or histological remission were considered in isolation, one-quarter of patients with quiescent IBD continue to meet Rome III criteria for IBS.[11] In contrast to the general population, where the reported prevalence of IBS ranges from 5-10%,[16] these data suggest that the prevalence of IBS is significantly higher in individuals with IBD, and should prompt clinicians to exert a high level of caution when considering escalation of therapy based on patient-reported measures in isolation, a strategy now supported by clinical practice guidelines for RCTs.[3]

Proposed aetiology of IBS-type symptoms in individuals with IBD

Visceral hypersensitivity is believed to be a key determinant of abdominal pain in IBS. Although its origins are uncertain, an exaggerated enteric immune system response to microbiome dysbiosis, increased bacterial lipopolysaccharides in the intestinal lumen, resulting in stimulation of afferent nerve endings then propagating the sensation of pain through spinothalamic, spinoreticular, and spinomesencephalic tracts to the thalamus, may be implicated in its develoment.[60] Adverse psychological health is associated with visceral hypersensitivity in IBS,[61] perhaps due to generation of a stress response through common pathways in the limbic system.

Reduced bacterial diversity and a pro-inflammatory microbiome are associated with disease activity in IBD, and murine models of colitis demonstrate that such alterations can sensitise nociceptive neurons and induce visceral pain.[62] However, in the only study that has compared the composition of the microbiome in patients with asymptomatic quiescent IBD with those reporting IBS-type symptoms, no significant difference in alpha or beta diversity was identified.[63] Observational studies examining the relationship

between IBS-type symptom reporting and psychological co-morbidity have highlighted a clear association,[64] and a recent meta-analysis suggests that higher rates of anxiety, depression, and somatisation are all associated with the presence of IBS-type symptoms.[11]

Another plausible explanation for the prevalence of IBS-type symptoms in quiescent IBD is the presence of persistent subclinical inflammation. Infective enteritis remains the strongest independent predictor of developing IBS,[13] and although no consistent biological marker for IBS has been demonstrated, raised levels of circulating pro-inflammatory cytokines, including IL-6 and TNFα, are seen in patients with IBS compared with healthy controls, both of which are implicated in the pathophysiology of IBD.[65] A case-control study comparing the levels of pro-inflammatory cell infiltrates, intestinal permeability, and TNFα expression between groups of patients with IBS, quiescent IBD with IBS-type symptoms, and healthy controls undergoing colonoscopy identified increased intestinal permeability in both groups compared with healthy controls, but increased levels of pro-inflammatory cells and TNFα expression only in patients with IBD.[66] Another study of patients with UC in deep remission identified higher circulating cytokine levels in patients with quiescent disease and IBS-type symptoms than asymptomatic patients.[67] The findings of these studies would suggest that persistent subclinical inflammation in IBD could be the cause for IBS-type symptoms. However, a third case-control study of 166 patients grouped into active UC determined by endoscopic Mayo score, quiescent UC with IBS-type symptoms, asymptomatic quiescent UC, IBS, and healthy controls, identified that irrespective of inflammation or the presence of IBS-type symptoms, the inflammatory profiles of patients with UC are different to those with IBS, suggesting that although subclinical inflammation may be present in IBS, it is part of a separate inflammatory process, and the presence of IBS-type symptoms in patients with IBD should not be considered a consequence of subclinical disease activity.[68] Studies comparing FC levels in patients with quiescent IBD support these

findings, suggesting no difference in the levels of inflammation between asymptomatic patients and those reporting symptoms compatible with IBS.[69, 70]

Disease outcomes according to the presence of IBS-type symptoms

The presence of IBS-type symptoms in quiescent IBD is associated with a reduced quality of life and increased healthcare utilisation; the latter potentially due to a lack of recognition of the likely aetiology of these symptoms, which results in unnecessary investigations.[69, 71] Despite the high prevalence of IBS-type symptoms, there is no apparent association with adverse disease outcomes in IBD.[69, 72] Current treat-to-target recommendations have shifted in recent years to acknowledge the poor correlation between disease activity indices and underlying inflammation in patients with IBD, and now recommend that symptom reporting alone should not be considered sufficient to guide treatment decisions in IBD, but instead should be used in conjunction with objective assessments of disease activity, such as FC measurement.[73] The routine application of FC in clinical practice to affirm patient-reported symptoms may enable earlier identification of IBS-type symptoms in quiescent disease, and avoid unnecessary investigations and treatment.

TREATMENT OF PSYCHOLOGICAL CO-MORBIDITY AND IBS-TYPE SYMPTOM REPORTING IN IBD

Conventional IBD therapies

Extensive RCT evidence supports the efficacy of 5-aminosalicylic acids, immunomodulators, biologics, and small molecules for the induction and maintenance of

mucosal healing in IBD.[74, 75] However, their impact on the psychological health of patients with active IBD is relatively unstudied. A prospective study of newly diagnosed patients with CD commencing infliximab therapy reported not only reduced clinical activity scores, but also reduced anxiety and depression scores, and increased quality of life scores 30 weeks after commencing therapy.[76] Similar findings have been reported for UC patients receiving adalimumab.[77] Given the inflammatory theory of depression, it is possible that these improvements in mood are due to direct effects of anti-TNFα treatment on mood, rather than an improvement in mucosal inflammation and GBA-mediated effects. Despite this, an RCT comparing infliximab with placebo in 60 patients with depression without a diagnosis of IBD identified no significant improvement in depressive symptoms between those treated with anti-TNFα compared with placebo.[78] Furthermore, similar findings have been reported for vedolizumab, with a small observational study suggesting a reduction in disease activity and mood scores for both infliximab and vedolizumab, with no evidence of superiority for either drug.[79] Unlike anti-TNFα therapies, vedolizumab is a gut-selective therapy, binding selectively to α4β7 integrin, blocking its interaction with MAdCAM-1, which is mostly expressed on gut endothelial cells, thereby preventing lymphocytes entering the gastrointestinal tract and reducing inflammation. It is, therefore, more likely that the improvement in anxiety and depression symptoms reported in these studies is because of GBA-mediated effects, rather than direct effects on the CNS. None of these studies utilised objective assessments of disease activity, instead relying on clinical disease activity indices. To date, no studies have examined the efficacy of biologic therapies in patients with quiescent IBD reporting IBS-type symptoms, and there are no data in patients with IBS.

Manipulation of the faecal microbiome

Microbiome-directed therapies, including probiotics, which are living microorganisms that promote growth of the normal gut microflora, prebiotics, high fibre-containing supplements intended to nourish these microflorae, and symbiotics, a combination of the two, have all been tested in IBD. All preparations are safe and well-tolerated, but existing RCTs are small and meta-analyses have suggested significant heterogeneity between studies.[80, 81] Nevertheless, there does appear to be evidence that the probiotic VSL#3 may be as efficacious as mesalazine in maintaining remission in UC patients with quiescent disease.[81] When comparing the effects of all three treatments, symbiotics appear to exert the greatest effect, potentially inducing remission in UC.[80] The majority of RCTs have a short duration of follow-up, and the long-term outcomes with these therapies are unclear. Moreover, few studies have attempted to correlate any improvement in symptom reporting with a comparative assessment of microbiome composition before and after treatment. Although the findings of a recently published meta-analysis suggest probiotics are also effective in alleviating diarrhoea in IBS,[82] only two observational studies have sought to assess their effect in patients with persistent symptoms in otherwise quiescent IBD. The first, an observational study of 43 patients with UC in endoscopic remission meeting the Rome IV criteria for IBS, suggested an improvement in diarrhoeal symptoms and quality of life.[83] These findings are supported by the second, a pilot RCT examining the effects of a probiotic treatment for patients with quiescent CD meeting Rome III criteria for IBS.[84] No improvement in mucosal inflammation, defined by measurement of FC, was observed, but a significant improvement in anxiety scores was noted, suggesting that manipulation of the gut microbiome may improve psychological health in these patients.[76] The validity of this study is limited by its small sample size of only 11 patients, and further research assessing the effect of probiotics on psychological health in patients with IBD who report IBS-type

symptoms would be welcome, particularly as some RCTs of probiotics in IBS have demonstrated small, but significant, improvements in depression and anxiety scores when compared with placebo.[85]

A variety of herbal remedies may manipulate the gut microbiome. Small RCTs examining the effect of curcumin as a complimentary treatment for UC have demonstrated improvements in mucosal healing for those with active UC when administered alongside mesalazine.[86] Furthermore, a recently published RCT comparing the use of curcumin with qing-dai, versus placebo, for patients with active UC reported a ≥1-point reduction in Mayo score in 75% of patients at week 8 of therapy versus 20% of those in the placebo group, suggesting that there may be a role for such therapies in IBD if subsequent larger RCTs demonstrate similar findings.[87] However, no studies have been conducted in patients with quiescent IBD who report IBS-type symptoms.

A meta-analysis of the available RCTs examining the effects of faecal microbiota transplantation (FMT) in patients with IBS has demonstrated symptomatic benefits when administered by the colonic route.[88] Similarly, a meta-analysis of RCTs examining FMT in 324 patients with UC reported short-term improvements in both clinical and endoscopic scores with a similar safety profile to placebo.[89] Many of the studies included in this meta-analysis had a short duration of follow-up and, to date, only one study by Sood *et al.* has attempted to establish the role of subsequent FMT in maintaining remission in UC.[90] This pilot study examined the effects of FMT versus placebo in 61 patients with quiescent UC and suggested significant improvements during 48 weeks of follow-up in those receiving FMT. However, this study was conducted alongside standard medical treatments, which limits the strength of the findings. Only one RCT of FMT versus sham transplantation has been conducted in CD, recruiting 17 patients, and although endoscopic improvements were seen in patients undergoing FMT, patients who flared during the study received escalation of medical

therapy, which is a significant confounding factor.[91] Furthermore, there were no significant alterations in gut microbial composition in the treatment group, making it is difficult to conclude that these patients truly responded to the FMT rather than an escalation of medical therapy. To our knowledge, no studies have examined the effect of FMT on mood in IBD. However, studies examining the effects on gastrointestinal symptoms and mood in patients with IBS, indicate improvements in both gastrointestinal symptoms, and symptoms of anxiety and depression, in those treated with FMT, suggesting that FMT may be beneficial for patients reporting IBS-type symptoms.[92, 93] The role of FMT as a treatment for IBS-type symptoms in quiescent IBD, however, has not been assessed and, currently, its use in both IBS and IBD remains experimental. Current IBD management guidelines suggest its use be restricted to concurrent *Clostridium difficile* infection in UC.[73]

Dietary therapies

Current guidelines support the use of a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) as a first line treatment to reduce the volume of luminal water and gas associated with visceral pain in IBS.[61] A low FODMAP diet results in increased bacterial diversity for patients with IBS,[94] which may further explain its success in reducing symptoms.[95] Three RCTs have attempted to clarify whether a low FODMAP diet has similar benefits for patients with quiescent IBD reporting IBS-type symptoms.[96-98] Positive findings have been suggested by all three, including an increase in the number of patients reporting adequate symptom relief, improvement in quality of life, and reduction in biochemical activity, as defined by FC measurement.[98] These studies are all small, however, and despite promising findings, their results requires conformation in larger trials before guidelines can recommend their use in IBD. However, as a low FODMAP diet is

safe, its use could be considered for patients with quiescent IBD and IBS-type symptoms. Other dietary therapies, including adopting a Mediterranean diet, have shown promise in the management of IBS and associated psychological co-morbidity, but this has not been tested in IBD.[99]

Brain-gut behavioural treatments

Brain-gut behavioural treatments work to enable individuals to recognise troubling emotions, thoughts, or behaviours, and modify them. A detailed review of each of the available therapies is beyond the scope of this review, but their methods are summarised in Table 1. In the context of gastrointestinal symptoms, manipulation of the GBA using these treatments aims to reduce the symptoms associated with DGBI and has a good evidence base in IBS,[26] with brain-gut behavioural treatments now advocated in national guidelines as an adjunct to medical therapies in select cases.[100]

The evidence pertaining to the efficacy of brain-gut behavioural treatments in patients with IBD, however, is less clear. A recent meta-analysis of RCTs has examined the effects of brain-gut behavioural treatments on disease activity and several parameters of psychological health, including anxiety, depression, perceived stress, and quality of life in IBD.[101] Overall, brain-gut behavioural treatments do not appear to exert beneficial effects on disease activity in IBD. However, short-term improvements in anxiety, stress, and quality of life scores were identified as well as sustained improvements in depression scores, with third wave therapies currently having the largest evidence base. Given the existing evidence that the prevalence of psychological co-morbidity is highest during periods of disease activity, it is perhaps disappointing that only four RCTs, to date, examined the effect of brain-gut behavioural treatments in patients with active disease.[102-105] Furthermore, RCTs in IBD continue to recruit

undifferentiated patients, rather than those with symptoms of a common mental disorder, and this appears to be where the greatest evidence base for these treatments lies.[101, 106] Despite the proven efficacy of brain-gut behavioural treatments in IBS, only one RCT, to date, has examined the effects of a brain-gut behavioural treatment in patients with quiescent IBD reporting IBS-type symptoms, and although the results suggested this was effective in this subgroup of patients, with only 27 patients included, limited conclusions can be drawn regarding their efficacy in this patient group.[107] Further RCTs are needed to determine if brain-gut behavioural treatments can improve disease outcomes, particularly in those with known psychological co-morbidity, and patients with quiescent IBD reporting IBS-type symptoms.

Gut-brain neuromodulators

Antidepressants, traditionally used in the treatment of mental illness, are now better referred to as gut-brain neuromodulators, given that their pharmacological properties extend beyond their actions on the brain. They are proven to improve abdominal pain IBS,[27, 108] and as with brain-gut behavioural treatments, their use is advocated in current treatment guidelines for IBS.[100] The mechanism by which gut-brain neuromodulators are believed to alleviate gastrointestinal symptoms is through the upregulation of neurotransmitters, including corticotropin releasing factor, serotonin, and norepinephrine, which are key determinants of visceral sensitivity and motility.[109] In the case of IBD, it is also suggested that neuromodulators exert anti-inflammatory effects, via modulation of pro-inflammatory cytokines, and their direct effects on neurogenesis, intracellular cyclic adenosyl monophosphate production, serotonin metabolism, and the hypothalamic pituitary adrenal axis.[110] A meta-analysis of 603 depressed individuals supports this theory, demonstrating that

selective serotonin reuptake inhibitors affect both IL-6 and TNF-α, both of which are implicated in the immunopathogenesis of IBD.[111]

Studies conducted in murine models of quiescent colitis have demonstrated that inducing depression results in reactivation of mucosal inflammation, which can be mitigated by pre-administering gut-brain neuromodulators,[112] and furthermore that the administration of tricyclic antidepressants can improve colonic inflammation, even in the absence of depressive symptoms.[113] Results of a large epidemiological study including over 400,000 individuals identified that those with depression had an increased risk of developing IBD, which is reduced in patients exposed to gut-brain neuromodulators for other medical reasons, suggesting that the use of gut-brain neuromodulators may be a protective factor.[114] Another large registry-based study of almost 43,000 patients identified lower rates of disease activity among patients with UC and CD newly commencing gut-brain neuromodulators, when compared with patients who did not. However, the strength of these observations is limited by the lack of clinical data to confirm disease outcomes, instead using proxy measures to determine IBD activity using clinical codes.[115]

RCTs examining the effect of gut-brain neuromodulators on disease activity in IBD are sparse, in comparison with those conducted in individuals with DGBI, with only two reported in the literature.[116, 117] Neither study recruited a selected cohort of patients with regard to the presence of psychological co-morbidity at baseline. Duloxetine was found to reduce both clinical disease activity scores, and anxiety and depression scores, in addition to improving quality of life scores, compared with placebo, in 44 patients with IBD.[116] Conversely, fluoxetine was found to exert no effect on each of these outcomes compared with placebo in 26 patients with CD.[117] A systematic review and meta-analysis of 13 RCTs by Wang *et al.,*[118] comparing the use of gut-brain neuromodulators versus placebo in 884 patients with IBD, found that gut-brain neuromodulators reduce anxiety, depression, and

disease activity scores, in addition to improving quality of life. However, all but the two aforementioned trials included were conducted in China, which may limit the generalisability of these conclusions. Furthermore, although most studies recruited selected patients, either with anxiety or depression at inclusion, subgroup analyses were not performed to determine if gut-brain neuromodulators performed better in individuals who had evidence of a common mental disorder.[118]

There remains only one retrospective study examining the effects of gut-brain neuromodulators in patients with persistent symptoms despite disease quiescence in IBD. This study reported a moderate improvement in symptoms in at least 60% of patients when amitriptyline was administered, versus placebo.[119] These findings mirror the benefits seen in a large RCT of amitriptyline in the treatment of IBS.[27] A summary of the evidence base for these treatments is outlined in Table 2.

Other pharmacological therapies

Although the reporting of IBS-type symptoms in quiescent IBD does not appear to alter the disease course, they are associated with comparable increases in healthcare utilisation and negative effects on quality of life to active IBD, which makes them an important treatment target.[72, 120] Treating the presence of these symptoms separately, as concurrent IBS, therefore could be an appropriate strategy.

Loperamide is a μ-opioid receptor agonist, which serves as an anti-diarrhoeal agent by decreasing intestinal smooth muscle contractions. It is considered a first-line treatment in IBS with diarrhoea to achieve symptom control,[100] as well as in grade 1 (mild) checkpoint inhibitor colitis,[121] suggesting that its use is safe in the presence of even mildly active inflammation. No trials have been conducted in patients with quiescent IBD. However, by

inference, anti-diarrhoeal agents could be considered safe for symptomatic relief in patients with IBD with ongoing diarrhoea, after exclusion of disease activity by objective assessment. Antispasmodics, such as hyoscine butylbromide or peppermint oil, which acts directly on intestinal smooth muscle to induce relaxation, are considered safe for use in IBS,[108] and are included in current treatment algorithms to alleviate pain.[100] To date there are no studies examining their effects in active or quiescent IBD with IBS-type symptoms but given their favourable safety profile, guidelines now advocate trialling them in this context, providing an objective assessment of disease activity has first been performed.[122]

Finally, the 5-hydroxytryptamine-3 receptor antagonist ondansetron has been studied in IBS with diarrhoea and has demonstrated significant improvements in stool consistency in RCTs, versus placebo.[123-125] A meta-analysis of the three available trials suggests ondansetron also reduces faecal urgency, but not abdominal pain.[123] Ondansetron has also demonstrated an association with reduced colonic damage, neutrophil infiltration, and colonic levels of pro-inflammatory cytokines in experimental colitis.[126] Although no studies have examined the effects of ondansetron in patients with IBD with IBS-type symptoms, a RCT examining the effect of ramosetron, an alternative 5-hydroxytryptamine-3 receptor antagonist, on pain and stool frequency in IBD patients reporting IBS-type symptoms, suggested a benefit of this treatment.[127]

DISCUSSION

Recent medical advances, including the implementation of FC as a non-invasive biomarker to assess inflammatory activity non-invasively, and the discovery of multiple effective biological therapies to treat mucosal inflammation, have transformed the management of IBD substantially over the last two decades. Although the decline in the

number of IBD-related surgeries certainly attests to the success of modern medical therapies, this review highlights a subgroup of patients for whom conventional therapies do not address their ongoing issues. One-third of patients with quiescent IBD experience persistent gastrointestinal symptoms, which suggests that patient-reported symptoms cannot be considered synonymous with underlying mucosal inflammation in IBD, and alternative explanations must be sought for the presence of these symptoms. Concurrent IBS certainly seems to be a plausible explanation for these symptoms, and perhaps considering IBS-type symptoms as a separate entity in quiescent IBD is necessary. This would enable clinicians to treat these patients symptomatically, within existing guidelines.

The high prevalence of common mental disorders in IBD highlighted in this review, and their adverse effects on disease outcomes, healthcare utilisation, and quality of life demonstrates that there is now very little doubt that the GBA exerts bi-directional effects in IBD and underscores the importance of addressing mental health in routine IBD care, moving more towards a biopsychosocial model. The evidence emphasised in this review, however, has yet to translate into clinical practice, with IBD guidelines continuing to focus almost exclusively on the inflammatory aspect of the disease. This is likely due to a combination of finite healthcare resources and a lack of understanding as to who to offer these treatments to. Possible future directions are summarised in Table 3.

The recognition that basing an assessment of disease activity solely on patient-reported symptoms contributes to poor care, and recommendation that physicians should base their decisions not only on clinical assessment, but alongside an objective assessment of disease activity to delineate those with truly active disease represents a major development in IBD. These measures are likely to further delineate the subgroup of patients discussed in this review. However, in a disease where treatment guidelines offer very few suggestions pertaining to the management of symptoms not arising from inflammatory activity, it is

imperative that researchers now turn their focus to identifying effective therapies in this large subgroup of patients. Trials of GBA-directed therapies in patients with psychological co-morbidity, along with studies examining the efficacy of proven IBS treatments in patients with quiescent disease with IBS-type symptoms, are required before guidelines can be restructured to meet the needs of a substantial minority of patients with IBD.

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Table 1: A Summary of the Available Brain-gut Behavioural Treatments to Treat Gastrointestinal Symptoms.

Intervention	Concept of therapy	Third wave	Talking therapy
Cognitive behavioural therapy	Aims to identify problematic thinking styles and where they arise in daily life. Work towards modifying these thoughts to improve mood and alleviate anxiety.	No	Yes
Mindfulness	Aims to identify how patients experience certain moments and equip them with the skills to consciously redirect their attention to other aspects of the triggering experience.	Yes	Yes
Acceptance and commitment therapy	Combines mindfulness with CBT strategies to allow increased flexibility when dealing with stressful events.	Yes	Yes
Hypnotherapy	Induction of deeply relaxed state to try and alter habits.	No	No
Psychodynamic psychotherapy	Identifies unconscious processes that manifest in the individual's behaviour, to promote self-awareness and understanding of how past experiences influence present behaviour.	No	Yes
Solution-focused therapy	Focuses on setting goals and creating steps to achieve them, focusing on what can be achieved rather than what cannot.	No	Yes

Table 2: A Summary of the Evidence Base for Current Interventions in IBD Including in Patients with IBS-type Symptoms and Common Mental Disorders.

	Specific therapy	**Type of study**	**Tested in patients reporting IBS-type symptoms**	**Tested in patients with common mental disorders**
Biological therapies	Anti-TNFα antibodies Anti-integrin antibodies	RCTs[76, 77] RCT[79]	Indirectly: poor clinical response in symptomatic patients with low inflammatory burden.[54-56]	Indirectly: improvement in mood scores in IBD.[76, 77, 79]
Microbiome therapies	Probiotics	Meta-analysis of RCTs[80, 81]	Yes: improvement in diarrhoeal symptoms and quality of life scores.[83]	No
	Prebiotics	Meta-analysis of RCTs[80]	No	No
	Symbiotics	Meta-analysis of RCTs[80]	No	No
	Curcumin Curcumin and qindai	Meta-analysis of RCTs[86] RCT[87]	No	No

	Faecal microbial transplant	Meta-analysis of RCTs for UC.[89] Single pilot RCT for CD.[91]	No	No
Dietary therapies	Low FODMAP diet	RCTs[96, 97]	Yes: reduction in IBS symptom severity and improved quality of life scores.[96, 97]	No
GBA-directed therapies	Gut-brain neuromodulators including selective serotonin re-uptake inhibitors, serotonin and norepinephrine re-uptake inhibitors, and tricyclic antidepressants	Meta-analysis of case-series and RCTs[118]	Possibly: improvements in gastrointestinal symptoms when used in conjunction with optimised medical therapy for UC.[119]	No

	Brain-gut behavioural treatments including CBT, mindfulness, acceptance and commitment therapy, hypnotherapy, psychodynamic psychotherapy, and solution-focused therapy.	Meta-analysis of RCTs[101]	Yes: improvement in quality of life scores in one RCT.[107]	Yes: improvement in depression scores in one RCT.[106]

Table 3: Possible future directions.

	Gap in literature	Future research	Measure	Patient subgroup
GBA Modulation	The role of neuromodulators in IBD.	RCTs examining the efficacy of neuromodulators versus placebo.	Objectively measured disease activity/ Psychological health	Individuals with adverse psychological health.
	The role of psychological therapies in IBD.	RCTs examining the efficacy of psychological therapies versus placebo	Objectively measured disease activity/ Psychological health	Individuals with adverse psychological health.
Microbiome Manipulation	The role of probiotics, prebiotics, and symbiotics in IBD.	RCTs examining the efficacy of these therapies versus placebo	Gastrointestinal symptoms /objectively measured disease activity.	Individuals with objectively measured quiescent disease and meeting criteria for IBS.
				Patients with objectively confirmed disease activity.
	The role of a low FODMAP diet in IBD.	RCTs examining the efficacy of a low FODMAP diet versus diet as usual on gastrointestinal symptoms reporting.	Gastrointestinal symptoms.	Patients with objectively confirmed quiescent disease and meeting criteria for IBS.

FIGURE LEGENDS

Figure 1: The Neurohormonal Pathways of The Gut-Brain Axis