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TITLE PAGE

Title: The Influence of the Brain-Gut Axis in Inflammatory Bowel Disease, and Possible Implications for Treatment.

Short running head: Targeting the Brain-Gut Axis in IBD.

Authors: David J. Gracie, PhD[1], P. John Hamlin, PhD[1], Professor Alexander C. Ford, MD[1,2].

[1]Leeds Gastroenterology Institute, St. James's University Hospital, Leeds, UK.

[2]Leeds Institute of Biomedical and Clinical Sciences, University of Leeds, Leeds, UK.

Correspondence: Dr. David J Gracie

Leeds Gastroenterology Institute

Room 125

4th Floor

Bexley Wing

St. James's University Hospital

Beckett Street

Leeds

United Kingdom

LS9 7TF

Email: djgracie1982@doctors.org.uk

Telephone: +441132684963

Facsimile: +441132429722

Abbreviations:

CBT	cognitive behavioural therapy
CD	Crohn's disease
CRP	C-reactive protein
FC	faecal calprotectin
FMT	faecal microbiota transplantation
FODMAP	fermentable oligosaccharides, disaccharides, monosaccharides, and polyols
GI	gastrointestinal
HPAA	hypothalamus-pituitary-adrenal axis
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
RCT	randomised controlled trial
TNF	tumour necrosis factor
UC	ulcerative colitis

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ABSTRACT

Brain-gut interactions influence the natural history of psychological wellbeing and symptom-reporting in functional gastrointestinal (GI) disorders; the presence of anxiety or depression is associated with the development of new onset GI symptoms, and the presence of GI symptoms is associated with the development of psychological disorders de novo. In inflammatory bowel disease (IBD), the reporting of irritable bowel syndrome (IBS)-type symptoms in patients with quiescent disease is common, and is associated with psychological disorders, impaired quality of life, and increased healthcare utilisation. In IBD, data from observational studies suggest that psychological disorders may be associated with relapse of disease activity, and that inflammatory activity is associated with the development of new psychological disorders, as has been described in functional GI disorders. The brain-gut axis provides the physiological link between central nervous system and GI tract that may facilitate these relationships. In IBS, treatments targeting disordered brain-gut axis activity, including psychological therapies and antidepressants, may lead to improved symptoms and quality of life. However, in IBD, the benefit of these treatments is less certain, due to a lack of interventional studies. Despite this, observational data suggest the impact of disordered brain-gut axis activity in IBD is substantial, and there remains scope for further well-designed trials of psychological therapies and antidepressants, particularly in a sub-set of patients who suffer from co-existent psychological disorders, or those who report IBS-type symptoms. Integrating these treatments into a biopsychosocial model of care has the potential to improve both psychological wellbeing and quality of life in some patients with IBD, reducing healthcare utilisation, and altering the natural history of these diseases.

INTRODUCTION

The inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory disorders of the gastrointestinal (GI) tract, which have a substantial impact on quality of life. Symptoms attributable to these conditions include abdominal pain, increased stool frequency, and the passage of blood per rectum. The natural history of IBD is that of periods of quiescence interspersed with episodic flares of disease activity, and its treatment is becoming increasingly personalised. Historically, assessment of disease activity has been based on the interpretation of patient-reported symptoms, with escalation of medical therapy occurring in response to the presence of presumed inflammation. Despite this, the relationship between GI symptom-reporting and the presence of objectively quantified active mucosal inflammation is poor.[1,2] Accordingly, reliance on subjective measures of assessment of disease activity, based on patient-reported symptoms, may result in inappropriate escalation of therapy in patients without objective evidence of inflammation.[3]

This may be due, in part, to the relatively high proportion of patients with IBD who report persistent GI symptoms, often compatible with irritable bowel syndrome (IBS) (Panel 1), in the absence of inflammation. Investigating the prevalence and impact of these type of symptoms in patients with IBD has been the subject of multiple recent research efforts. In patients with quiescent disease, it is estimated that around 10% report frequent abdominal pain,[4] and between 11% and 35% report IBS-type symptoms,[5-8] distinct from ongoing, continuous abdominal pain that is unrelated to defaecation, with a higher prevalence in CD compared with UC. Even among patients with IBD in histological remission, almost one-in-three meet criteria for IBS.[7] Moreover, there appears to be a consistent association between reporting of abdominal pain or IBS-type symptoms and impaired psychological wellbeing,[4,6] and this relationship is durable over time.[9]

Psychological disorders, including anxiety and depression, affect more than 30% of patients with IBD.[10] Most studies in IBD have assessed anxiety and depression using self-report measures, which provide only an indication of these conditions. This should not be confused with a formal diagnosis of generalised anxiety disorder or major depressive disorder. A diagnosis of generalised anxiety disorder requires presence of excessive anxiety and worry about a variety of topics, events, or activities, present for at least the last 6 months, which is challenging to control, and associated with at least three other common symptoms of anxiety, such as irritability or poor concentration.[11] Major depressive disorder requires that an individual experience a persistent low mood or loss of interest for at least 2 weeks, with at least five other common symptoms associated with depression, such as hopelessness, poor sleep, and decreased appetite.[11] Of relevance to patients with IBD is that it can also manifest with physical symptoms, such as chronic pain.

Although the aetiology of IBD is incompletely understood, several contributory factors may influence disease activity including smoking, poor diet, lack of physical exercise, host genetic factors, and a pro-inflammatory intestinal microbiome. More recently, the relationship between psychological co-morbidity and inflammatory activity has garnered considerable interest. The pathophysiological mechanisms underpinning these relationships remain speculative, but disordered brain-gut axis activity could contribute. For instance, observational studies suggest that antecedent psychological co-morbidity may be associated with adverse outcomes in IBD during longitudinal follow-up,[12-19] and also that inflammatory activity is associated with the de novo development of psychological disorders.[20-22] In addition, a recent study suggests that these relationships may be bi-directional.[23] These bi-directional brain-gut pathways have been described previously in people with functional GI disorders,[24,25] and centrally acting treatments in functional GI disorders can improve symptoms and quality of life.[26-29] Whether targeting these potential mechanisms will improve

both psychological wellbeing and disease outcomes in IBD is less certain. To date, clinical trials of therapies targeting psychological disorders in IBD have shown limited benefit,[30,31] but the number of studies examining this issue is small, and limitations in their design impacts the findings.

This review discusses the complex relationship between symptom-reporting, inflammatory activity, and psychological wellbeing in IBD, highlighting the possible role of the brain-gut axis in these relationships, and summarising current evidence for the management of brain-gut axis dysfunction in IBD. Although this is a widely accepted paradigm in functional GI disorders it is, perhaps, less well-recognised in IBD. Emphasising limitations in current understanding of the role of pharmacological and psychological therapies directed at brain-gut dysfunction in IBD may help to inform the design of randomised controlled trials (RCTs) of these treatments in the future.

SEARCH STRATEGY AND SELECTION CRITERIA

We searched and reviewed MEDLINE, EMBASE, and EMBASE Classic using the terms “inflammatory bowel disease”, “irritable bowel syndrome”, “pathophysiology”, “psychological wellbeing”, “anxiety”, “depression”, and “brain-gut axis” in order to identify relevant publications describing the pathophysiology of IBS-type symptoms, and the relationship between psychological wellbeing and disease activity, in adults with IBD until December 2018. We included only publications in English, and selected publications suitable for this review based upon the novelty and impact that these new data appear to have for contemporary and emerging concepts of pathophysiology. We also searched clinicaltrials.gov for ongoing or recently completed RCTs in this field. Out of 3000 publications that were identified initially, we selected publications whose findings were, in our view, of the greatest importance.

SYMPTOM-REPORTING IN THE ABSENCE OF INFLAMMATION: THE IBD-IBS INTERFACE

Given that the correlation between symptom-reporting and objectively confirmed mucosal inflammation in IBD is poor,[1,2] factors other than inflammatory activity are likely to contribute to the generation of GI symptoms in IBD. The presence of symptoms in the absence of inflammation has often been attributed to co-existent IBS. When faced with patients who report these symptoms, the clinician encounters significant difficulty in disease assessment and management, particularly if clinical decision-making is made on the basis of patient-reported symptoms in isolation.[3] Escalation of therapy in this situation is appealing, particularly as a treat-to-target approach, using presence of patient-reported outcomes, such as rectal bleeding and diarrhoea, is recommended by expert opinion.[32] However, use of immunomodulator therapies or biological agents can be associated with infective and neoplastic complications,[33,34] increased healthcare costs, and may not be effective in this patient group.[35-37] Improved understanding of the prevalence, aetiology, and impact of IBS-type symptom-reporting in IBD may help to develop an evidence base for targeted interventions in these patients, which are much needed.

Prevalence of IBS-type Symptom-reporting in IBD

In a previous systematic review and meta-analysis of 13 observational studies, one-in-three patients with UC, and almost 50% of patients with CD reported symptoms compatible with IBS.[5] The odds of reporting IBS-type symptoms in patients with IBD felt to be in clinical remission was more than four-fold that of healthy controls. However, the majority of these studies did not use an objective measure of intestinal inflammation to confirm quiescent disease, such as faecal calprotectin (FC). This is likely to have resulted in an over-estimate of the prevalence of these types of symptoms. Three subsequent studies that used FC to exclude

active disease prior to labelling patients as reporting IBS-type symptoms, defined using the Rome II in one study and the Rome III criteria in two studies, demonstrated generally lower rates of symptom-reporting, between 11% and 31%.[6-8]

Proposed Aetiology of IBS-type Symptoms in IBD

The prevalence of symptoms meeting criteria for IBS is 11% in the general population,[38] but appears to be almost three times higher in patients with IBD in some studies. Although the aetiology of both IBD and IBS is uncertain, pathophysiological mechanisms responsible for the development of these conditions may be similar. Mucosal inflammation is pathognomonic of IBD. However, subclinical mucosal inflammation and increased mucosal barrier permeability may play a role in the development of IBS. Studies have demonstrated increased levels of circulating pro-inflammatory cytokines in both the peripheral blood and intestinal mucosa of patients with IBS,[39] when compared with controls. The role of subclinical mucosal inflammation in the development of IBS-type symptoms in IBD is conflicting. In one prospective case-control study,[40] pro-inflammatory cell infiltrates, enhanced tumour necrosis factor (TNF)-α expression, and increased paracellular permeability were observed in patients with IBD who reported IBS-type symptoms. However, other observational studies suggest that the inflammatory burden, measured using FC, is no greater among patients with IBS-type symptoms than in asymptomatic patients with quiescent IBD.[2,7,8] Furthermore, presence of IBS-type symptoms does not appear to have any adverse impact on longitudinal disease activity,[9] which one might expect if occult, untreated inflammation was the underlying cause.[41]

In IBS, bacterial lipopolysaccharide-mediated enteric immune activation, consequent visceral hypersensitivity, and afferent sensory nerve stimulation is thought to result in activation of the brain-gut axis.[42] This mechanism may also be relevant in IBD; reduced

bacterial diversity and a pro-inflammatory bacterial microbiome are associated with disease activity.[43] However, the only study to examine the microbiome in patients with IBD reporting IBS-type symptoms failed to identify any significant difference in the abundance of individual bacterial taxa, or in overall bacterial diversity, between those who reported IBS-type symptoms and those who did not.[44] Despite this, involvement of the brain-gut axis may still play a substantial role in the development of these symptoms, as has been described in IBS.[24,25] Psychological disorders, including anxiety and depression, are associated with IBS-type symptom-reporting,[6,45] and this relationship appears durable over time.[9] The presence of psychological disorders in patients with IBD could therefore be a risk factor for the development of IBS-type symptoms, and these relationships might be mediated via brain-gut axis dysfunction.

PSYCHOLOGICAL DISORDERS AND THE BRAIN-GUT AXIS IN IBD

The brain-gut axis is a term used to describe the complex interaction between neuroendocrine pathways, the central, peripheral, and autonomic nervous systems, and the GI tract (Figure 1). These inter-connected pathways are thought to be instrumental in the pathophysiology of functional GI disorders, where presence of brain-gut interactions are demonstrated by the generation of new GI symptoms in people with pre-existing psychological disorders, whilst presence of gut-brain interactions are supported by the de novo development of anxiety or depression in people who already report GI symptoms. Simultaneous brain-to-gut and gut-to-brain activity highlights the role of bi-directional brain-gut axis interactions in IBS,[24,25] and other chronic GI disorders.

A detailed description of the complex mechanisms that underpin the brain-gut axis is beyond the scope of this review. In brief, psychological disorders may influence GI function via the generation of a stress response, which results in activation of the hypothalamus-pituitary-adrenal axis (HPAA). The impact of HPAA activity includes direct effects of

adrenocorticotropic hormones on the GI tract, such as increased intestinal permeability, which has been observed in murine models of stress,[46] and increased secretion of glucocorticosteroids. Increased sympathetic autonomic activity observed in stressed individuals is associated with enhanced secretion of catecholamines, including epinephrine and norepinephrine from the adrenal medulla. The combination of increased catecholamine secretion and increased sympathetic outflow may have pro-inflammatory effects on the GI tract, via stimulation of mast cells and macrophages, with inflammatory cytokines mediating these effects.[47,48]

The increase in intestinal permeability associated with the stress response may also allow the gut microbiota to interact with the nervous system; the so-called microbiota-brain-gut axis. In mouse models of colitis changes in psychological wellbeing and behaviour appear to be related to gut microbial composition, and can be attenuated by probiotics.[49,50] These effects are vagally-mediated, and the vagus nerve is thought to have a direct anti-inflammatory role, via cholinergic inhibition of pro-inflammatory cytokines,[51] but these parasympathetic reflexes are diminished during the stress response. Consequently, low vagal tone, which can be monitored via heart rate variability, has been associated with higher levels of TNFα and salivary cortisol,[52] and a pilot study suggested that vagal nerve stimulation induced clinical and endoscopic remission in some patients with IBD.[53] Whether monitoring vagal tone as a means of predicting relapse of disease activity is feasible is unclear.

In addition to the involvement of neuroendocrine pathways, which may be enhanced by stressful stimuli, afferent sensory nerve fibres are involved in the propagation of painful stimuli in a gut-to-brain direction. The aetiology of visceral hypersensitivity in IBD is uncertain, and visceral hypersensitivity is not always reproducible between individual study populations,[54-56] but may involve abnormal enteric immune system activation in response to exposure to luminal bacterial lipopolysaccharide, arising secondary to increased GI

permeability. In terms of response to visceral pain, perception is thought to involve the spinothalamic, spinoreticular, and spinomesencephalic tracts.[57] The convergence of each of these pathways may involve the limbic system, with evidence from animal models providing a feasible link between visceral hypersensitivity of the GI tract and emotional distress and psychological disorders.[58]

Epidemiology of Psychological Disorders in IBD

Psychological co-morbidity, including anxiety and depression, is common in patients with IBD, with observational studies reporting a prevalence of up to 35%.[10] A previous systematic review and meta-analysis reported that there was moderate evidence that these rates were higher than among healthy controls, and that rates were higher among those with active, compared with inactive, disease.[59] Risk factors for the development of psychological disorders in IBD include disease activity, an aggressive phenotype, and female sex.[20,59] Distinct from any potential direct negative impact on disease activity, it is proposed that the presence of psychological disease may have other deleterious consequences. These include lower adherence to medical therapy,[60] and increased frequency of investigation requesting and clinic attendance. In one small study of patients with IBD with co-existent psychological disorders who were administered an antidepressant, number of relapses of disease activity, need for glucocorticosteroids, and number of investigations requested were all significantly reduced in the 12 months after commencement of the antidepressant, compared with the 12 months prior to commencement.[61]

The Impact of Psychological Wellbeing on Disease Activity in IBD

In a previous systematic review and meta-analysis of observational studies examining the impact of psychological co-morbidity on disease outcomes in IBD, Alexakis et al.

reported that depression was not associated with flare of disease activity during longitudinal follow-up.[62] However, only four studies were included in the formal meta-analysis. The authors identified seven other studies, five of which did demonstrate a significant association between antecedent psychological disorders and subsequent disease activity. In addition to these, a large registry-based observational study, not included in this systematic review, has also suggested that psychological co-morbidity may impact negatively on disease course during longitudinal follow-up.[18] Finally, other investigators have demonstrated heightened response to psychological stressors in patients with IBD,[48] and that stressful life events may precede flares of disease activity.[15,63]

This relationship between psychological wellbeing and disease activity, independent of the reporting of IBS-type symptoms, suggests that brain-gut axis dysfunction may also be implicated in the propagation of disease activity in IBD, mediated by aberrant brain-gut interactions. However, a major limiting factor in the examination of the temporal relationship between psychological disorders and longitudinal disease activity in many studies conducted to date is the lack of objective quantification of subsequent inflammatory activity. Most investigators have examined the impact of pre-existing psychological co-morbidity, including depression, anxiety, perceived stress, or a stressful life event on the natural history of IBD using clinical disease activity indices only. There have been three studies using a combination of clinical disease activity indices and endoscopic assessment that examined the longitudinal relationship between stress and depression in less than 200 patients with UC in total,[13,15,17] but follow-up in two of these studies was only 1 year.[15,17] The lack of large observational studies assessing the impact of psychological disorders on the natural history of IBD that utilise objective measures of inflammatory activity to confirm disease activity highlights the deficiencies in our understanding of the temporal relationship between the two.

The Impact of Disease Activity on Psychological Wellbeing in IBD

Three longitudinal studies have sought to investigate gut-brain interactions in IBD.[20-22] Of these, two described a detrimental impact of active disease at baseline on subsequent psychological wellbeing, with an increased incidence of new-onset anxiety and depression during longitudinal follow-up ranging from 6 months to 8 years,[20,21] but the third reported no impact of disease activity on subsequent psychological wellbeing.[22] Together, these data provide some evidence for the existence of gut-to-brain interactions in IBD. However, inherent limitations in their design include the fact that two of the studies based their assessment of baseline disease activity on clinical measures only,[21,22] and the third used a retrospective case note review to determine the presence of inflammatory activity, and its impact on longitudinal outcomes.[20] Although brain-gut interactions may explain disease activity having implications for future psychological wellbeing other explanations, which have been less well-studied, include catastrophising, hypervigilance concerning GI symptoms, symptom-specific anxiety, and abnormal regulation of emotions.[22,64] In addition, perceived stigma, social isolation, and the necessity to make substantial lifestyle changes when IBD is active may also contribute.[65,66]

Psychological Wellbeing and Disease Activity in IBD: A Bi-directional Relationship?

Experimental mouse models of colitis support the existence of a bi-directional relationship between psychological wellbeing and GI inflammation.[67-69] Inducing GI inflammation is associated with the onset of behavioural changes,[67] and the presence of depression can reactivate colonic inflammation,[68] which may be reversed by the use of antidepressants.[69] In humans with IBD, psychological stress is associated with increase serum and mucosal inflammatory cytokine expression,[70] and it has been reported that the use of biological agents may be associated with improved depression scores.[71] In addition, as some

patients with depression exhibit elevated levels of pro-inflammatory cytokines, there is the potential for patients with IBD to enter into a vicious cycle, where active disease induces a psychological disorder, whose inflammatory component propagates disease activity.[72]

Only two prospective observational studies have sought to examine bi-directional brain-gut interactions in IBD.[23,73] In the first of these, Sexton et al. conducted a longitudinal 6-month follow-up study of 369 patients with IBD.[73] Following multivariate regression, their results supported the existence of a bi-directional relationship between clinical disease activity, but not inflammation, and perceived stress in CD. In a similar study of 405 patients with IBD, conducted over a minimum follow-up period of 2 years, the hazard ratio for both flare of disease activity and escalation of medical therapy in patients with anxiety and quiescent disease at baseline, confirmed by FC, was more than twice that of patients with quiescent disease who did not report symptoms of anxiety.[23] In the same study, the presence of symptomatic disease at baseline was associated with a more than five-fold increase in the risk of developing anxiety de novo.

TREATMENT OF IBS-TYPE SYMPTOMS AND PSYCHOLOGICAL CO-MORBIDITY IN IBD

In patients with IBD, mucosal inflammation, psychological co-morbidity, and the presence of IBS-type symptoms are all associated with poor quality of life.[6] The presence of anxiety or depression may adversely impact on the natural history of IBD, which in turn may worsen psychological wellbeing,[23] and result in further impairment of quality of life. Subclinical mucosal inflammation, an abnormal microbiome, and disordered brain-gut axis activity may be implicated in the development of IBS-type symptoms and psychological co-morbidity in IBD. Thus, the use of immunomodulators, probiotics, faecal microbiota transplantation (FMT), antidepressants, and psychological therapies would all seem logical

approaches to managing this clinical scenario. A summary of the evidence base for these interventions is provided in Table 1. Ongoing RCTs in this field that have yet to report are summarised in Table 2.

Conventional Pharmacological Therapies

Numerous RCTs investigating the effect of pharmacological therapies, including glucocorticosteroids, 5-aminosalicylic acids, immunomodulators, and biological therapies, have been conducted in IBD. However, end-points in these studies have focused exclusively on their effect on disease activity, largely using clinical disease activity indices until relatively recently. Although none of these trials has reported the efficacy of such treatments on the management of IBS-type symptoms specifically, some RCTs of biological therapy have commented on the lack of efficacy of these treatments in symptomatic patients with IBD who did not have objective evidence of inflammatory activity, such as an elevated C-reactive protein (CRP), at randomisation.[35-37] These findings suggest that conventional pharmacological therapies are not effective in the management of symptomatic patients in whom the inflammatory burden is limited and presumably, by extrapolation, patients with IBD who report IBS-type symptoms. A RCT of infliximab for treatment-resistant depression did not demonstrate any beneficial effect overall, although those with a high CRP at baseline appeared to have a larger improvement in depression scores.[74]

The proposed pathophysiological mechanisms by which psychological co-morbidity and inflammatory activity may be inter-related are discussed above. Psychological disorders are associated with increased circulating pro-inflammatory cytokines and CRP,[75] supporting the observation that treatment with immunosuppressants may impart beneficial effects on psychological wellbeing, independent of their effects on inflammatory activity. In IBD, observational studies of patients with CD and UC newly-commenced on either anti-TNFα

therapy or vedolizumab have demonstrated improved depression scores following treatment.[71,76] However, neither of these studies accounted for the potential confounding effect of glucocorticosteroid tapering on psychological wellbeing in their analyses.

Manipulation of the Intestinal Microbiome

Probiotics may be effective for the treatment of persistent GI symptoms and depression in IBS.[77,78] A recent meta-analysis of RCTs has also examined their effects in IBD.[79] Their efficacy, in terms of induction of remission of active disease, or prevention of relapse of quiescent disease, was limited, and none of the trials sought to determine the effect of probiotics on either psychological wellbeing or IBS-type symptoms. In non-IBD populations, the effect of probiotics on psychological wellbeing has been studied in a recent meta-analysis of 10 RCTs.[80] The authors concluded that there was a lack of evidence to support the use of probiotics for depressive symptoms, and that the inclusion of studies of depressed and non-depressed populations in the same analyses, as well as the use of varying strains and treatment regimens, limited the ability to draw valid conclusions.

FMT remains an experimental intervention in IBD, although a meta-analysis of RCTs suggests that it may be an effective treatment in active UC.[81] However, its use as a treatment for IBS-type symptoms in patients with IBD has not been evaluated. In an observational study of FMT in patients with IBS, active treatment was associated with an improvement in depression scores, which was associated with an increase in faecal microbial diversity.[82] A recent RCT of FMT, versus a placebo of the patient's own faeces, in IBS demonstrated a significant improvement in symptoms in patients treated with FMT at 3 months, suggesting that further RCTs may be worthwhile, although this was not sustained at 12 months.[83]

A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) is recommended as a first-line treatment for IBS.[84] FODMAPs are

osmotically active fermentable carbohydrates, the ingestion of which results in increased luminal water and gas volume,[85] leading to the perception of pain, but only in selected patients with visceral hypersensitivity.[86] The low FODMAP diet is also associated with alterations in bacterial diversity, specifically the abundance of Bifidobacteria.[87] In an open-label trial of 89 patients with IBD, who also fulfilled the Rome III criteria for IBS, participants were randomised to a low FODMAP or normal diet.[88] The investigators reported higher rates of improvement in IBS-type symptoms and quality of life in patients receiving the low FODMAP diet, when compared with those eating a normal diet. In a double-blind cross-over, re-challenge RCT, 32 patients with IBD with functional symptoms, who had previously responded to a low FODMAP diet, were randomised to a series of 3-day FODMAP challenges, during which time symptom severity and stool output were assessed.[89] Pain, bloating, flatulence, and faecal urgency scores were all significantly higher on day 3 of the FODMAP challenge, compared with day 3 of a control challenge with glucose. An RCT of a low FODMAP diet versus sham dietary advice in 52 patients with quiescent IBD who reported functional bowel symptoms, which has been published recently in abstract form, demonstrated significantly higher rates of adequate relief of symptoms with a low FODMAP diet. [90] Although these RCTs, and other observational studies, investigating the relationship between FODMAPs and IBS-type symptom-reporting in patients with IBD highlight a potential therapeutic role for the low FODMAP diet, the lack of large-scale RCTs limits the validity of these findings in clinical practice.

Antidepressants

Antidepressants, when used at low dose to regulate brain-gut activity, have more recently been referred to by experts in the field as neuromodulators.[28] The proposed mechanisms by which they may impart beneficial effects in IBD are two-fold. These include

the induction of vagus nerve-mediated anti-inflammatory effects,[69] but also a potentially direct effect on pro-inflammatory cytokines. This may arise via action on the nuclear factor-κB and nitric oxide pathways, which are both implicated in the aetiology of IBD.[91] In a large registry-based study, including almost six million primary care patients, with follow-up conducted over a median period of 6.7 years, the presence of depression was associated with an increase in incident diagnoses of both CD and UC.[92] The authors also noted that the risk of developing IBD was attenuated by the use of antidepressant medication, suggesting that targeting psychological disorders may have a beneficial impact on the disease course in patients with an established diagnosis of IBD. In another observational study of patients with quiescent IBD and pre-existing anxiety, there was a trend towards a reduction in the need for escalation of medical therapy in those prescribed antidepressants, particularly selective serotonin re-uptake inhibitors.[93]

A previous systematic review and meta-analysis that assessed the impact of antidepressants in IBD reported a beneficial effect of antidepressants on disease activity in 12 of 15 studies, and an improvement in depression and anxiety scores was observed in eight of nine studies reporting these outcomes.[31] However, the majority were retrospective and observational in design. There was one RCT of duloxetine identified, recruiting 44 patients,[94] in which depression, anxiety, and symptom scores were significantly lower, and quality of life scores significantly higher, in those receiving duloxetine compared with placebo. A pilot RCT of fluoxetine in 26 patients with CD has also been conducted,[95] but this did not demonstrate any benefit in terms of maintenance of disease remission, or psychological wellbeing, although the trial was underpowered to detect any difference in either of these outcomes.

Only one study has reported the efficacy of tricyclic antidepressants in patients with IBD, who reported ongoing symptoms in the absence of objectively quantified inflammatory

activity.[96] Although patients in this retrospective uncontrolled study were not screened formally using validated questionnaires to confirm whether or not they met symptom-based criteria for IBS, there was at least a moderate improvement in symptoms in 60% of patients, with a greater response in patients with UC, compared with CD. The degree of symptom response in patients with IBD was similar to that observed in a control group of patients with IBS who were also commenced on tricyclic antidepressants.

Psychological Therapies

In addition to antidepressants, psychological therapies, including cognitive behavioural therapy (CBT) and gut-directed hypnotherapy, are of benefit in some patients with IBS,[29] and are recommended by national management guidelines.[84] Only one RCT has sought to examine the effect of psychological therapy specifically in patients with IBD reporting IBS-type symptoms.[97] The authors reported that multi-convergent therapy was associated with an improvement in quality of life, when compared with a waiting list control. Despite this, the sample size of only 27 patients means that definitive evidence to support the efficacy of psychological therapies in this patient group is lacking.

A recent meta-analysis of 14 RCTs of psychological therapies, which recruited 1196 patients with IBD, examined their effect on disease activity, anxiety, depression, perceived stress, and quality of life.[30] Therapies assessed in individual trials included CBT, psychodynamic therapy, stress reduction, and hypnotherapy. Overall, in patients deemed to have quiescent disease at baseline, there was a statistically significant improvement in depression scores, and a significant improvement in quality of life scores, in those receiving psychological therapy over placebo. When individual psychological therapies were assessed, CBT led to a significant improvement in quality of life scores. Overall, psychological therapies did not appear to have any beneficial effects on disease activity. However, the

inclusion of patients with IBD without psychological disorders in the trial populations may have resulted in an underestimate of the effect of these interventions. Although there is evidence to suggest that stressful live events may precede flares of disease activity, there has been only one trial of a behavioural intervention to improve coping skills,[98] and this did not assess the effect of this approach on disease activity formally.

Other Pharmacological Therapies

Diarrhoea is likely to be the predominant symptom pattern associated with the reporting of IBS-type symptoms in IBD. Despite this, the use of anti-diarrhoeal agents including loperamide, diphenoxylate, and codeine is cautioned against, particularly in those with active disease.[99] No study has described the effect or safety of any of these medications in patients who report IBS-type symptoms. A RCT of the 5-hydroxytryptamine-3 receptor antagonist ondansetron, conducted in patients with diarrhoea-predominant IBS, demonstrated improvements in urgency, stool frequency, and stool form, when compared with placebo.[100] However, its efficacy in patients with IBD reporting IBS-type symptoms has not been studied.

PERSPECTIVES

The diagnosis and management of IBD has evolved significantly in recent decades. Observational studies assessing disease outcomes in IBD have demonstrated a decline in the incidence of surgery, presumably secondary to the development of novel therapeutic agents during this time.[101] Although the advent of FC, and other non-invasive markers of disease activity, has allowed physicians to define disease activity more objectively, experts now advocate a treat-to-target strategy, where escalation of therapy is considered in patients on the basis of ongoing symptoms.[32] The fact that as many as one-in-three patients with no evidence

of mucosal inflammation still report GI symptoms highlights that current available treatments remain suboptimal in a substantial subgroup of patients. Despite this, the focus of contemporary medical intervention is centred almost exclusively on the treatment of inflammatory activity.

Deconstructing the complex relationships between symptom-reporting, inflammatory activity, psychological co-morbidity, and co-existent IBS-type symptoms in IBD highlights that current treatment algorithms, which fail to address many of these problems specifically, are suboptimal. Previous proposals for a biopsychosocial model for the management of IBD have not resulted in a change in current best practice.[102] A recent white paper from the American Gastroenterological Association highlighting the importance of the psychosocial needs of patients with IBD,[103] together with improved understanding of the role of the brain-gut axis in IBD underline how important it is to develop individualised, integrated management strategies, which simultaneously address both inflammatory activity and psychological wellbeing, for a subgroup of patients (Figure 2).

Although interventions including psychological therapies, specifically CBT, a low FODMAP diet, and antidepressants show some promise for the treatment of psychological disorders and IBS-type symptoms in IBD, data supporting their use as adjunctive measures for the treatment of active disease, or maintenance of disease remission are lacking. RCTs of these treatments have relied upon patient-reported symptoms as the sole determinant of disease activity at randomisation and follow-up, making interpretation of their findings unreliable. Moreover, the inclusion of patients without psychological disorders or IBS-type symptoms in these trials is likely to have resulted in an under-reporting of their efficacy.

Evidence suggests that psychological stressors, and the stress response, may play a role in disease activity via the brain-gut axis, but there is a lack of research specifically addressing the impact of anxiety and/or depression on inflammation. Other features of

reduced psychological wellbeing, such as anhedonia and loss of interest in usual activities, or even perceived stress itself, may affect adherence to treatment and engagement with hospital appointments,[104,105] thus impacting on the disease course. In addition, it is likely that the prevalence of generalised anxiety disorder and major depressive disorder in patients with IBD is lower than the prevalence of self-reported depressive and anxiety symptoms in the studies summarised in this article.

Nevertheless, the possibility that brain-gut axis dysfunction influences both psychological wellbeing and the natural history of IBD, in a bi-directional manner, highlights the importance of this potential pathophysiological mechanism when considering novel interventions in IBD. There remains scope for further well-designed RCTs of treatments targeting the brain-gut axis, particularly in more carefully selected groups of patients. These could include those at risk of developing psychological disorders, those with pre-existing anxiety or depression, as a means of preventing relapse of disease activity, or those who report co-existent IBS-type symptoms in the absence of inflammation, in order to reduce symptom burden and improve quality of life. Currently, evidence for the routine use of psychological therapies, antidepressants, and treatments targeting the intestinal microbiome in all these groups of patients is limited. Despite this, data implicating the influence of the brain-gut axis on disease course are accumulating, and treatments successfully targeting this mechanism have the potential to improve both psychological wellbeing and quality of life in some patients with IBD, as well as to assist in altering the natural history of these disorders.

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AUTHORS CONTRIBUTIONS

DJG performed the literature search. DJG, PJH and ACF drafted the manuscript. All authors contributed to and approved the final draft of the manuscript.

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ETHICS COMMITTEE APPROVAL

Not required.

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Panel 1. The Rome IV Criteria for Irritable Bowel Syndrome.

≥ 6 month history of recurrent abdominal pain occurring, on average, at least 1 day per week in the last 3 months, associated with 2 or more of:

1. Relieved or aggravated by defecation;
2. A change in frequency of stool;
3. A change in form (appearance) of stool.

Table 1: Evidence Base for the Treatment of IBS-type symptoms and Psychological Disorders in Patients with IBD.

	Type of study	Specific therapy identified as effective	Tested in patients reporting IBS-type symptoms	Tested in patients with psychological disorders
Biological therapies	RCTs[35-37]	Anti-TNFα	Indirectly (lack of response in symptomatic patients with low inflammatory burden)[35-37]	No
Probiotics	Meta-analysis of RCTs[79]	VSL#3 in UC only	No	No
Faecal microbial transfer	Meta analysis of RCTs[81]	Not applicable	No	No
Low FODMAP diet	RCTs[88,89]	Low FODMAP diet	Yes (improved quality of life and IBS symptom severity[88,89])	No
Antidepressants	Meta-analysis of case-series and RCTs[31]	Selective serotonin re-uptake inhibitors, serotonin and norepinephrine re-uptake inhibitors, and tricyclic antidepressants	Possibly (patients with ongoing symptoms despite "adequate" therapy for UC[96])	No

Psychological therapies	Meta-analysis of RCTs[30]	CBT	Yes (improved quality of life in sub-group analysis in one RCT[97])	Yes (no effect over waiting list control in one RCT[97])

Table 2: Ongoing Clinical Trials of Interventions in Patients with IBD Reporting IBS-type Symptoms, or With Co-existent Psychological Disorders.

Intervention (NCT number)	Study population	Tested in patients reporting IBS-type symptoms	Tested in patients with psychological disorders	Outcomes to be assessed
Low FODMAP diet (NCT02469220)	Patients with UC in remission fulfilling Rome IV criteria for IBS	Yes	No	IBS symptom severity Generic quality of life Pain scores
Low FODMAP diet **Ondansetron** **Amitriptyline** **Loperamide** [106]	Patients with UC in remission with persistent diarrhoea	Potentially	No	Gastrointestinal symptoms Disease-specific quality of life Disease activity Anxiety and depression scores
Internet-based CBT (NCT03852745)	Patients with IBD with high anxiety, depression, or perceived stress scores	No	Yes	Perceived stress Anxiety and depression scores
Mindfulness-based cognitive therapy (NCT03162575)	Patients with IBD in remission with elevated fatigue scores	No	No	Fatigue scores Anxiety and depression scores Disease-specific quality of life

Internet-based CBT (NCT03327038)	Patients with IBD with high anxiety or depression scores	No	Yes	Anxiety and depression scores Disease activity Disease-specific quality of life

Figure 1: Proposed Neuroendocrine Pathways Involved in the Brain-Gut Axis.

Figure 2: Biopsychosocial Model for Inflammatory Bowel Disease.