Common mental disorders in irritable bowel syndrome: pathophysiology, management, and considerations for future randomised controlled trials

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The frequent co-occurrence of irritable bowel syndrome and the common mental disorders of anxiety and depression is well established. A range of biological and psychosocial disease mechanisms are common to both disorders, many of which contribute to a dysregulated gut–brain axis. Clinical and subthreshold psychological comorbidity adds to the functional impairment and disease burden in individuals with irritable bowel syndrome. Progress is being made with regard to understanding irritable bowel syndrome in the clinical setting from a biopsychosocial perspective. However, until now, most trials of irritable bowel syndrome treatment still consider the disease as a gut disorder in isolation, which leaves major gaps in knowledge about disease–disease interactions and treatment outcomes in irritable bowel syndrome. In this Viewpoint, we review the epidemiology, pathophysiology, and management of anxiety and depression in individuals with irritable bowel syndrome. We also provide methodological recommendations for future randomised controlled trials and outline guidance for research that better incorporates psychiatric comorbidity into its design, with a view to improve treatment outcomes for individuals with irritable bowel syndrome.

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Introduction

Irritable bowel syndrome (IBS) is a functional bowel disorder that is characterised by recurrent abdominal pain and altered stool form or frequency. Diagnosis is based on the Rome IV criteria.[1] Treatment usually aims to target the most bothersome gastrointestinal symptom. A high number of individuals with IBS have a common mental disorder co-existing with the peripheral gut symptoms.[2] The frequent co-occurrence of gastrointestinal and psychological symptoms in IBS has been attributed to overlapping genetic, physiological, early life, and psychosocial risk factors that alter functioning of the gut–brain axis.[3]

Anxiety and depression are common mental disorders. Anxiety disorders are ranked sixth on the list of leading disability causes, with over 260 million people affected worldwide.[4] WHO considers depression to be the greatest contributor to disability worldwide (affecting over 300 million people) and that it is likely to be responsible for 800 000 suicide deaths annually.[4] A *Lancet* Commission[5] has predicted that the global economic consequences arising from mental disorders will be US$16 trillion between 2010 and 2030.

According to the best known classification systems for mental disorders (Diagnostic and Statistical Manual of Mental Disorders [DSM-5] and International Classification of Diseases [ICD-10]), symptoms of anxiety include worry that is excessive and difficult to control, difficulty concentrating, irritability, restlessness, fatigue, muscle tension, and sleep problems, as well as symptoms or conditions specific to a particular anxiety subtype (eg, anxiety raised by a situation or object in phobias).[6,7] There are several types of anxiety disorder, including generalised anxiety disorder and obsessive-compulsive disorder, both of which are particularly prevalent in IBS.[8] Health anxiety (ie, preoccupation with, and fear of, physical symptoms of disease), by definition, is distinct from common mental disorders, a type of somatic symptom disorder that is also very common in IBS.[9] Symptoms of depression include low mood, loss of interest or pleasure in most activities, feeling worthless and reporting excessive guilt, decreased concentration, thoughts of death and suicide, weight changes, sleep difficulties, fatigue, and psychomotor agitation or retardation.[6,7] For a clinical diagnosis, the symptoms of these common mental disorders need to be present most of the time, on most days, and should substantially impair functioning. Importantly, the symptoms should not be attributed to other mental or physical conditions, which might make a diagnosis challenging when working with chronically ill populations or populations with multiple comorbidities. Moreover, even subthreshold symptoms are associated with substantial functional impairment and contribute to at least half of the total burden of psychiatric morbidity associated with anxiety and depressive disorders.[10]

Deeper insight is needed into the role of common mental disorders in the manifestation and progression of IBS, and the effect of comorbid anxiety or depression, or both, on IBS treatment outcomes. Notably, the measurement and reporting of psychological symptoms in randomised controlled trials (RCTs) of IBS, particularly for gut-directed treatments, is infrequent. This widespread inattention to psychological comorbidity could be a contributor to the suboptimal therapeutic effects observed in many RCTs of peripherally acting treatments in IBS, and to the continuing challenges with regard to managing IBS where standard medical and dietary management are not effective. In this Viewpoint, we review common mental disorders in the context of IBS, including pathophysiology and treatments, and provide methodological recommendations for RCTs, as well as propose areas for future research. Despite the coaggregation of a variety of mental disorder comorbidities with IBS, this Viewpoint

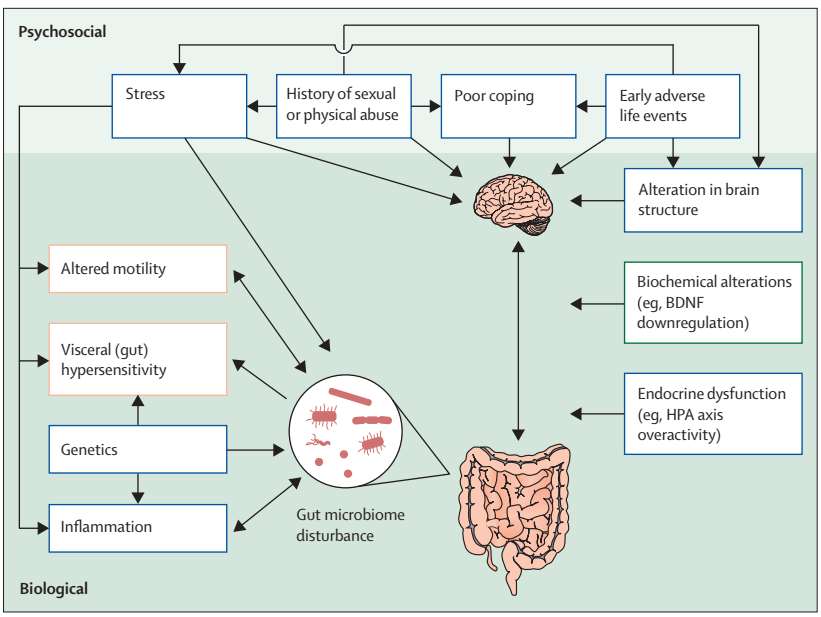

Figure 1: **Unique and overlapping factors in the pathophysiology of irritable bowel syndrome and common mental disorders**

A portrayal of some of the many interactions is shown (a comprehensive representation is not provided here). Numerous factors contribute to the pathophysiology of both irritable bowel syndrome and common mental disorders (including the microbiome, which is influenced by stress and inflammation) but might also perpetuate ongoing low-grade inflammation in these conditions. Orange boxes represent pathophysiological factors relevant to irritable bowel syndrome, green box represents pathophysiological factors relevant to depressive disorders and anxiety disorders, and blue boxes represent pathophysiological factors relevant to irritable bowel syndrome as well as depressive disorders and anxiety disorders. BDNF=brain-derived neurotrophic factor. HPA=hypothalamic–pituitary–adrenal axis.

focuses on the common mental disorders of anxiety and depression.

Epidemiology and burden of common mental disorders in IBS

Individuals with IBS have a risk of anxiety or depressive symptoms three times that of healthy individuals without IBS. In a systematic review and meta-analysis,[11] more than a third of individuals with IBS had anxiety symptoms and over a quarter had depressive symptoms, which was considerably higher than in healthy individuals. Subgroup analysis in this meta-analysis also showed a higher prevalence of anxiety and depressive symptoms in female individuals than in male individuals,[11] similar to non-IBS populations.[12] Although the overall prevalence of coexistent mental disorders in IBS has been evaluated rigorously, there are no prevalence data across ethnicities and sociodemographic variables. Compared with controls, not only is mental disorder comorbidity more common in people with IBS, but depressive symptoms are also more severe.[13] Further, although the prevalence of depression in IBS is equivalent to that in inflammatory bowel disease (an inflammatory and life-limiting condition that IBS is commonly mistaken for), depression presents as a more severe form in IBS,[14] probably due to the contribution of psychological factors to its cause, in addition to the burden of the gastrointestinal condition promoting psychological symptoms. Female sex and younger age are especially associated with a more severe depressive symptom profile.[13] Importantly, much of the literature reporting on mental health concerns in IBS is usually based on symptom screening with a questionnaire, which is not always concordant with a clinical diagnosis based on psychiatric interview. This aspect is an acknowledged limitation of research to date, including in other chronic gastrointestinal conditions,[15] and can lead to the overestimation of prevalence. In the context of this Viewpoint, we refer to the published literature, which is largely based on reporting symptomatology.

Gastrointestinal comorbidity, in terms of overlap of functional gastrointestinal disorders, and the presence of certain gastrointestinal symptoms, might also be important for increasing the chances of developing a common mental disorder. Observational secondary care data suggest that individuals with IBS who also have functional dyspepsia have an almost four times greater odds of reporting symptoms that are compatible with anxiety and depression than patients with IBS only, an important finding considering that, in this study, almost three-quarters of individuals with IBS had overlapping functional dyspepsia.[16] Prevalence of anxiety and depression also increases with the presence of specific co-existing symptoms, such as epigastric pain and urgency,[16] and prevalence of anxiety is higher in individuals with IBS with constipation, compared with other IBS subtypes.[11]

The burden of IBS is substantial and affects the individual, the health-care service, and the broader society, and has been well described. A concurrent mental disorder presents an inimitable additive burden that is increasing globally.[5] In IBS, psychological symptom severity is associated with more frequent use of health-care services and medication,[17] and more individuals with IBS who have a diagnosis of anxiety or depression, or both, report impairment in multiple domains of daily functioning, compared with those without this additional diagnosis.[18]

Pathophysiology of common mental disorders

The pathophysiology of common mental disorders is multifactorial and includes psychosocial and biological factors (figure 1), but elucidating the potential underlying mechanisms is the subject of intense research. Endocrine abnormalities, such as overactivity of the hypothalamic–pituitary–adrenal axis and oversecretion of cortisol,[19] and biochemical alterations, such as the downregulation of brain-derived neurotrophic factor, have been most consistently proposed as contributors to the cause of depression.[12] Reduced brain volume and alteration in resting brain functional connectivity (activity) across multiple brain regions might also be relevant,[12,20] and these same connectivity aberrations partly explain the structural brain differences between individuals with IBS and controls,[20] which is one of several overlapping, and

interacting, pathophysiological features in IBS and common mental disorders (figure 1). In addition to these biological factors, it has been suggested that up to 40% of the risk of depression is genetic,[12] and several psychosocial risk factors, including major life events and medical comorbidity, which have been studied extensively across many chronic disease contexts, are recognised as key contributors.

An important development in psychiatry is the identification that microbiome–gut–brain axis dysfunction, and specifically the microorganisms residing in the gut and their metabolites, is probably central to the cause of depression.[21] A substantial amount of evidence supports this working hypothesis. First, preclinical studies show the gut microbiome is important for gut–brain axis function at various levels, including brain neural activity, the hypothalamic–pituitary–adrenal axis, and modulation of the immune system.[22] Second, several human studies have reported differences in the faecal microbiome profile of individuals with depression, compared with healthy individuals, according to a recent systematic review and meta-analysis.[23] For example, several studies in the meta-analysis[23] reported that the family *Prevotellaceae* and genus *Faecalibacterium*, of which some members are beneficial short-chain fatty acid-producing species, are present in lower abundance in individuals with major depressive disorder compared with individuals without the condition. The microbial profile of individuals with IBS and psychological comorbidity can also be discriminated from those without comorbidity, either based on the overall profile of the microorganisms present,[24,25] or the lower alpha diversity.[26] However, despite many overlapping features of common mental disorders and IBS, there might be unique aspects of the aberrant microbial profile of psychological morbidity. Whether microbial differences in individuals with IBS and mental disorder comorbidity are due to greater gastrointestinal symptom severity or altered transit time, compared with individuals with IBS alone, is to be determined. Finally, preclinical studies have shown that faecal microbial transplantation from people who were depressed leads to inflammatory and anxiety-like behaviour in mice, compared with faecal microbial transplantation from healthy individuals.[22] Further supporting the microbiome as an important factor in mental disorder comorbidity in IBS, one study[27] has shown that the behavioural and gastrointestinal characteristics of individuals with anxiety and IBS are transferable to recipient mice via the microbiome. Low-grade inflammation and intestinal barrier dysfunction accompanied these changes and were proposed as potential mechanisms underlying the microbiome-induced dysfunction of the gut–brain axis. The role of systemic immune activation in the onset of depression is still a matter of debate. Nevertheless, these preclinical studies are valuable for verifying the causative role of the gut microbiome via several potential mechanistic pathways in common mental disorders and IBS. Evidence of efficacy of microbiome-targeted therapies in human trials of IBS and co-existing mental disorder comorbidity, which is discussed in this Viewpoint, further underlines the probable role of the microbiome in the pathophysiology of common mental disorders.

The overlap between gastrointestinal symptoms and anxiety or depression is not limited to IBS, and has been shown in non-clinical populations with mild symptoms, as well as in functional dyspepsia.[28] This finding suggests that the relationship does not require the presence of IBS-specific symptoms of pain and altered bowel habit per se. The sequence of gut–brain symptom onset might also provide signs to distinct underlying mechanisms of each disorder in patient subsets. For example, psychological comorbidity might increase vigilance to IBS symptoms and reduce visceral sensory thresholds, which increase the likelihood of gastrointestinal symptoms. Psychological symptoms initiated by mucosal barrier dysfunction and immune activation might also be important for brain-to-gut disease, particularly considering the evidence of a doubled susceptibility to postinfectious IBS in individuals with pre-existing anxiety symptoms, compared with those without pre-existing anxiety symptoms.[29] Conversely, population-based studies suggest that the gut drives (ie, gut symptoms preceed) psychological symptoms in half to two-thirds of individuals with a functional gastrointestinal disorder,[30,31] with peripheral abnormalities (such as an abnormal microbiome or immune dysregulation), or the distress related to physical disease, probably promoting psychological comorbidity.

Treatment of common mental disorders

In most health-care services, the first point of contact for a person experiencing symptoms of mental disorder is their primary physician (eg, general practitioner) who might provide psychoeducation and advice on lifestyle (eg, diet and exercise) and sleep hygiene in the first instance. For those with subclinical or subthreshold levels of depression or anxiety, self-help resources, including books, relaxation apps, and websites, are often recommended before psychotherapy or medication are considered. Psychological strategies are largely derived from cognitive behavioural therapy (CBT), a type of psychological treatment in which people are taught to challenge potentially unhelpful thinking patterns and modify behaviours. However, there are several other evidence-based psychotherapeutic interventions; for example, interpersonal therapy and other CBT-derived therapies (such as behavioural activation, acceptance commitment therapy, and mindfulness), which have been tested and reported to be effective in managing anxiety or depression, or both.[32]

For more serious presentations, referrals are made to mental health practitioners (eg, psychologists, social workers, or psychiatrists) for further assessment and possible treatment. Primary care physicians also often initiate treatment with antidepressants. The first-line

treatment is usually a selective serotonin reuptake inhibitor (SSRI), with tricyclic antidepressants (TCAs), serotonin–noradrenaline reuptake inhibitors (SNRIs), and atypical antidepressants used as second-line treatment. The decision on appropriate treatment is dictated by evidence-based guidelines and depends largely on the severity of symptoms. Some of the most influential guidelines for treating common mental disorders are those provided, and regularly updated, by National Institute for Health and Care Excellence (NICE).[33,34]

For people with moderate or severe depression, the NICE guidelines recommend a combination of antidepressant medication (with the dose titrated upwards, as required)[35] and a high-intensity psychological intervention.[33] For moderate to severe cases of anxiety, a choice of either high-intensity psychotherapy or drug treatment is recommended, which should be based on individual preferences, given that neither is superior to another.[34] For antidepressants, the SSRI sertraline is recommended as the most cost-effective drug.

The NICE guidelines provide separate recommendations for managing mental disorders in the context of chronic illness.[36] Collaborative patient-centred care is at the core of these guidelines, particularly in supporting more severe presentations. The recommendations for subthreshold and moderate depression resemble those for the general population, but NICE guidelines advise caution when prescribing antidepressants because potential interactions with other medications and side-effects influencing the physical disease need consideration.

Treatment of IBS with common mental disorder comorbidity

Preparing the patient

IBS is a condition that is characterised by complex bidirectional dysregulation of gut–brain interaction.[37] Therefore, gastrointestinal symptoms can influence psychosocial state, and vice versa. CNS processing of pain, and other gut signals, is required for the patient's subjective experience of symptoms. Therefore, treatment with an antidepressant or a CNS-targeted medication, termed central neuromodulators in this context,[38] or psychological therapy, such as CBT or gut-directed hypnotherapy, is a logical management option. However, screening for psychological symptoms in patients with symptoms that are viewed as physical is often not done,[39] despite the fact that co-existent mental disorders are associated with unmet patient expectations and worse quality of life, and increase the likelihood of provider frustration.[40,41] The reason for not screening for psychological symptoms might be due to clinical pressures, or the physician's skepticism, or unfamiliarity with efficacious treatments. Additionally, even if considered, there might be reluctance from patients to accept such treatments. This reluctance can occur due to an ineffective patient–provider relationship, with miscommunication as to the reason for selecting such therapies, or because patients might view them as stigmatising for what are predominantly physical symptoms.[42] There is also the potential for adverse events for certain pharmacotherapies;[43] although, in one RCT of the TCA desipramine, most symptoms attributed as the side-effects of the drug were present before treatment.[44] Additionally, careful co-ordination and communication of treatment plans is required when psychologists are also involved in patient care, and there is potential for this communication to break down.[45]

Although the presence of co-existent mental disorders might influence the decision to recommend these therapies, the patient's confidence in the treatment, relationship with the provider, and willingness to engage also influences effectiveness.[42,46] Studies have suggested that patients who are open to the use of such treatments, recognise the influence of mood on symptoms, and have time to participate, are more likely to respond than patients with severe psychological morbidities or personality disorder, those expecting a cure, or those who do not have time to commit to treatment.[46,47] It is also plausible that effectiveness will be influenced by the direction of symptom onset; individuals with a gut-to-brain direction of effect might have an improvement in mood with a peripherally acting drug that targets abdominal pain or bowel habit, whereas individuals with a brain-to-gut direction of effect might only respond to a central neuromodulator or behavioural therapy, or might require a combined approach of these treatments with a peripherally acting drug. However, this idea is speculative and is an area for future research.

Treatments

TCAs and SSRIs have effects on gastrointestinal function; TCAs slow gastrointestinal transit, whereas SSRIs accelerate it.[48,49] TCAs and SNRIs also have pain-modifying properties,[50,51] due to effects on norepinephrine transmission. SSRIs, which act solely by increasing 5-hydroxytrytamine neurotransmission, might have less effect on pain than TCAs and SNRIs,[52] but might be useful for treating co-existent anxiety or obsessive behaviours. TCAs are a logical choice for patients with IBS who have diarrhoea and abdominal pain as predominant symptoms, SSRIs might have additional benefit for constipation symptoms in patients with IBS and co-existent mental disorder, and SNRIs could be useful when abdominal pain is the dominant feature. Psychological therapies also have a dual gut–brain action. As well as effects on central processing within the prefrontal cortex (responsible for cognitive functions), basal ganglia, and limbic areas,[53] these therapies have effects on pain perception, visceral hypersensitivity, and gastrointestinal motility.[54,55] Figure 2 summarises treatments for IBS that might have a dual gut–brain action.

In a meta-analysis of 18 RCTs comparing TCAs or SSRIs with placebo in IBS, there was a significant benefit in favour of central neuromodulators (relative risk [RR]

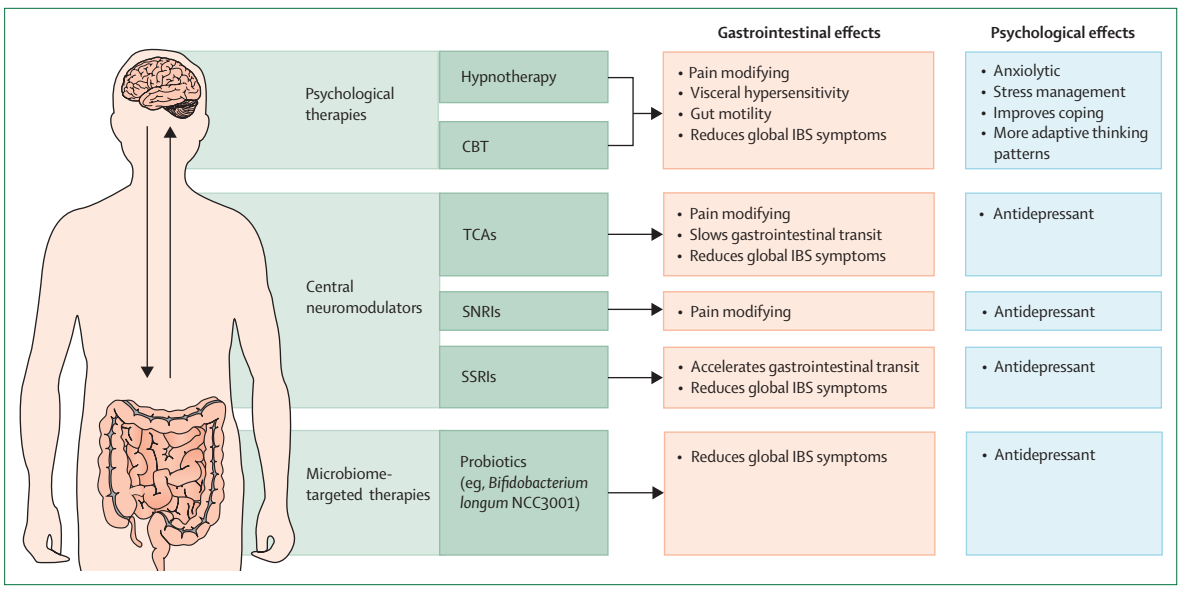

***Figure 2*: Treatments for irritable bowel syndrome with efficacy for gastrointestinal and psychological symptoms**
Although the specific biological effects leading to gastrointestinal outcomes are generally able to be elucidated through physiological testing and validated symptom questionnaires that assess pain, the mediators of psychological symptom improvement are less clear, and those listed are based on theoretical concepts. CBT=cognitive behavioural therapy. IBS=irritable bowel syndrome. SNRI=serotonin–noradrenaline reuptake inhibitor. SSRI=selective serotonin reuptake inhibitor. TCA=tricyclic antidepressant.

of IBS symptoms persisting 0·66, 95% CI 0·57–0·76).[43] However, only five trials examined efficacy according to the presence or absence of a co-existent mental disorder, and the results were conflicting. Although there is no evidence from RCTs to support the use of SNRIs in the management of IBS, this treatment is beneficial in other chronic painful disorders,[49] and there are reports of efficacy in some patients with IBS, particularly those with psychological comorbidity.[56] In terms of psychological therapies, in a network meta-analysis of all available treatments tested,[57] those with the greatest evidence for efficacy were self-administered or minimal contact CBT (RR of IBS symptoms persisting 0·61, 95% CI 0·45–0·83), face-to-face CBT (0·62, 0·48–0·80), and gut-directed hypnotherapy (0·67, 0·49–0·91).

For patients with psychological comorbidity who do not respond to these first-line therapies, combining or augmenting therapies is a reasonable approach. Meta-analyses support the use of combining central neuromodulators in the treatment of depression.[58,59] Although there are no RCTs of this approach in IBS, one case series has shown the benefit of adding quetiapine in patients with IBS who did not respond to a TCA or an SNRI.[60] Such synergistic effects are probably best achieved with drugs with complementary mechanisms of action (eg, a TCA for pain coupled with an SSRI for co-existent anxiety), but it is important to be aware of each drug's side-effect profile to minimise risk of serotonin syndrome, which is particularly likely with an SSRI and an SNRI combined. Some studies of depression and chronic pain disorders, such as tension headache, suggest that a central neuromodulator combined with a psychological therapy is more effective than either alone.[61,62] It might also be the case that augmentation with psychotherapy is only efficacious for specific subgroups, as has been hypothesised in inflammatory bowel disease.[63] Psychological therapy could improve adherence to treatment with central neuromodulators,[62] and the effect of improving the regulation of emotions with central neuromodulators on cognitive engagement with psychological therapy deserves further exploration.

Microbiome-targeted therapies also have some efficacy in common mental disorders. A meta-analysis of controlled clinical trials reported modest efficacy for probiotic supplementation for symptoms of depression and anxiety, with evidence of a greater effect size in clinical versus community samples. By contrast, prebiotic supplementation had no effect on symptoms of depression or anxiety, although fewer trials have been done.[64] Some preliminary evidence has shown that faecal microbial transplantation could be effective for depressive symptoms, although this evidence is limited to case reports of individuals with major depressive disorder.[65] Notably, two RCTs of faecal microbial transplantation in IBS, to date, have measured psychological symptoms as secondary outcomes, although both reported no effect on this endpoint.[66,67] The only RCT evaluating the effect of a microbiome-targeted intervention on psychological symptoms as a primary endpoint in IBS, although only a small pilot study, showed beneficial effects of *Bifidobacterium longum* NCC3001 in reducing depression scores.[68] Concurrent changes in amygdala activation and other relevant brain regions, and improvements in IBS symptoms, were reported, compared with placebo.

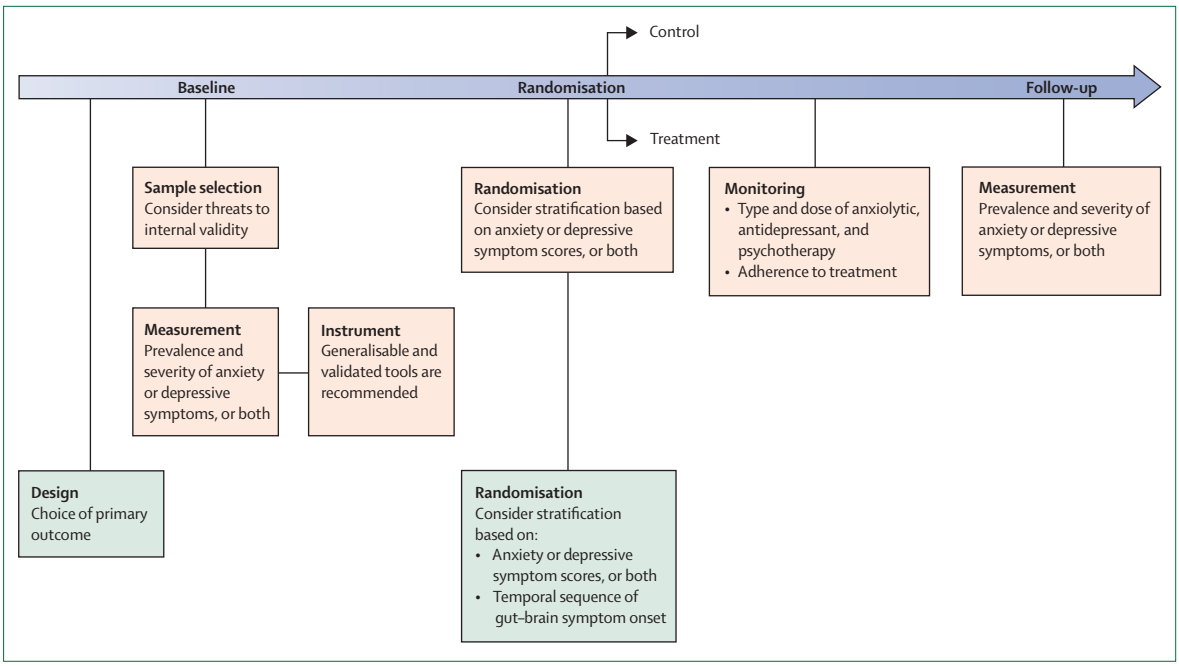

Figure 3: **Methodological recommendations for randomised controlled trials of irritable bowel syndrome across stages of an example parallel design trial**
Additional recommendations are provided that are specific to randomised controlled trials that specify co-existing anxiety or depressive symptoms as inclusion criteria. Where a clinical diagnosis of anxiety or depression is made via psychiatric interview (rather than measurement of anxiety symptoms or depressive symptoms, or both, by questionnaire), this is considered preferable for stratification purposes and should be used as baseline and follow-up measurements of prevalence or severity, or both. Red boxes represent the recommendations for randomised controlled trials of irritable bowel syndrome and green boxes represent the additional recommendations for randomised controlled trials of irritable bowel syndrome with coexisting anxiety or depressive symptoms, or both.

Relevance for research

Acknowledging mental disorder comorbidity in IBS management

From a biopsychosocial perspective, mental disorder comorbidity should be acknowledged in the management of IBS because it contributes to determining an individual's disease course and treatment outcome. The Multidimensional Clinical Profile framework published by the Rome Foundation clearly acknowledges this need by recognising IBS as a highly heterogeneous condition with frequent psychological comorbidity that influences a patient's experience of illness.[69] The framework provides detail on diagnostic criteria, risk factors, and so-called psychological red flags for clinicians that would indicate the consideration of a referral to a mental health professional.[69] Similarly, a best practice update by the American Gastroenterology Association provides recommendations for gastroenterologists for the assessment of psychiatric comorbidity and referral for gut–brain psychotherapies.[47] Specific information is provided to assist patient education about the gut–brain pathway and its role in IBS. Key points to explain the concept of psychotherapies and their underlying mechanisms of action are also provided, with a focus on the use of patient-friendly language. From a research perspective, RCTs investigating IBS as a single entity leave gaps in knowledge about its interaction with psychological comorbidity. Research should now aim to advance clinical practice; high quality RCTs that consider common mental disorder comorbidity in their design, implementation, and analysis are required to expose true treatment effects in both IBS alone and IBS with co-existent common mental disorders, and to refine current treatment algorithms.

Methodological recommendations for future RCTs

In this Viewpoint, we provide specific methodological recommendations for future RCTs in IBS as well as specifically for RCTs that specify co-existing anxiety or depressive symptoms as inclusion criteria (figure 3). First and foremost, reporting baseline prevalence, diagnosis, and symptoms of common mental disorders should become routine practice across all assessments of potential treatments for IBS (eg, drug, lifestyle, and dietary interventions). In rare situations, specific features of psychological comorbidity should be used as trial exclusion criteria if they pose a threat to internal validity; for instance, the presence of suicidal ideation. Second, measurement and reporting of anxiety and depression symptom severity before and after treatment should be considered, not only when there is rationale for the investigated treatment to affect these symptoms (eg, central neuromodulators) but also for secondary analysis in trials of gut-directed treatments (eg, a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols), because any improvement in

peripheral gastrointestinal symptoms might subsequently influence mood. Third, the tools used to measure mood symptoms should be generalisable to other chronic disease states (eg, the Hospital Anxiety and Depression Scale [HADS],[70] the Patient Health Questionnaire-9,[71] or the Generalised Anxiety Disorder-7 scale[72]). As an example, the HADS has been widely validated and there is minimal confounding by somatic symptoms.[73] However, despite being widely used in the literature concerning IBS, the HADS, Patient Health Questionnaire-9, and Generalised Anxiety Disorder-7 scale have limitations; they have not been validated specifically in IBS, and the validity of the HADS anxiety and depression subscales in other populations has been questioned.[74] Finally, strategies to account for confounding effects of co-existent mental disorder should be considered, including stratified randomisation, control and monitoring of concurrent anxiolytic and antidepressant therapy throughout the treatment period, and careful measurement of adherence.

Some additional recommendations should be considered for trials that consider specifying IBS and co-existing anxiety or depressive symptoms, or both, as key inclusion criteria. The focus on two comorbid conditions results in a conundrum: which should be the focus for the primary outcome (ie, gut or psychological symptoms). The research question and treatment under investigation will ultimately direct this decision. A coprimary outcome might be appropriate, although this will likely increase the sample size required. For studies that aim to examine underlying mechanisms of clinical response to treatment, phenotyping and stratified randomisation of patients based on the temporal sequence of gastrointestinal or psychological symptom onset will be important. Although a validated questionnaire to assess this consideration is not yet available, a simple question assessing onset and direction of symptoms could be used. Stratification by baseline psychological symptom severity should also be considered when data exist for its prognostic value, such as for CBT in which efficacy might be greater in people with less severe anxiety or depressive symptoms.[75,76]

Future research

There is still much to understand about the treatment needs of individuals with IBS and comorbid common mental disorders. Future research should focus on longitudinal studies to examine associations between psychological comorbidity and IBS outcomes, further testing of current treatments to evaluate gut–brain mechanisms of action, and assessing efficacy of novel treatments that have dual gut and brain effects. Even RCTs that only test treatments directed at the gut should report the effect on anxiety and depressive symptoms as outcomes. A minimum dataset of psychological symptom scores using standardised measures for all IBS treatment trials would facilitate direct comparisons of treatment efficacy. Conception and implementation of such RCTs will require involvement of multidisciplinary research teams consisting of gastroenterologists, psychologists, dietitians, and exercise physiologists.

Large scale phenotyping studies of individuals with IBS with and without comorbid mental disorders that measure a range of physiological, biological (eg, gastrointestinal function, microbiome), and psychosocial parameters will be required to uncover specific patient subgroups and point toward novel disease mechanisms that could be used to develop innovative targeted treatments. Recent research has reported the importance of psychological factors in the identification of subgroups of patients with IBS with the use of latent class analysis, suggesting that classifying patients with IBS and targeting treatment on the basis of gastrointestinal symptoms alone might not be sufficient.[77]

Longitudinal, prospective data for psychological and gastrointestinal symptoms from individuals with IBS and concurrent mental disorders will improve the understanding of the interactions between these two conditions. Additionally, these data could facilitate understanding of the effect of mental disorder comorbidity on the risk of developing IBS, on altering its natural history, on the overall cost and burden of IBS, and how mental disorder comorbidity moderates IBS treatment outcomes. Analysis of these data could be modelled on work in other chronic diseases, such as coronary heart disease, in which the interplay between physical and mental disorder comorbidity has been evaluated extensively.[78]

The effects of currently available central neuromodulators, alone and in combination with psychotherapeutic approaches, on psychological outcomes and gastrointestinal function requires further evaluation. Moderation analysis, such as that previously undertaken in CBT,[75] is needed to identify participant variables that predict response to treatments, which might help to progress precision medicine in IBS. Further study of the underlying mechanisms of efficacious treatments acting on both the gut and brain would help to distinguish the most important drivers of disease severity in individuals with IBS and common mental disorder comorbidity. Engaging individuals with IBS and common mental disorder comorbidity in qualitative research evaluating treatment preferences, and identifying challenges and barriers to care, will help determine the unique clinical needs of this group. Trial codesign and mixed methods trials with embedded qualitative components will facilitate research that is patient-centred and that measures outcomes that are important to the patients.

Prospective trials of patients receiving targeted treatments, based on mathematically modelled baseline symptom clustering (as described in a previous study[77]), compared with conventional care are needed. For example, clusters of patients with less severe gastrointestinal symptoms and more severe psychological

Search strategy and selection criteria

We searched for relevant articles published in English between Jan 1, 1980, and Aug 25, 2020, using MEDLINE, PubMed, Google Scholar, and references from relevant articles. We used the primary search terms "irritable bowel syndrome/IBS", "common mental disorder", "anxiety", "depression", "pathophysiology", and "treatment", alone or in combination. We considered articles relevant if they addressed human pathophysiology, burden, management, or research evaluation of IBS with concurrent common mental disorder.

comorbidity would likely receive a psychological therapy, clusters of patients with more severe gastrointestinal symptoms and less severe psychological comorbidity would likely receive a peripherally acting drug, and clusters of patients with more severe gastrointestinal symptoms and more severe psychological comorbidity would likely receive a combination of psychological therapy and drugs, including central neuromodulators. Assessment of this type of approach is necessary for further personalisation of care and improving clinical outcomes.

High quality trials of treatments with integrated action are scarce.[54,68] New adequately powered trials testing such treatments are needed and might encompass novel central neuromodulators, psychotherapeutic approaches, dietary therapies, or microbiome-targeted treatments. One pragmatic RCT of integrated gastroenterology care (including gut-focused hypnotherapists, dietitians, and psychiatrists), compared with standard gastroenterology only care, showed superiority in terms of improvement in gastrointestinal symptoms for patients with functional gastrointestinal disorders, with the added benefit of cost savings.[79] Further larger effectiveness trials of this multidisciplinary model of care in individuals with IBS and psychological comorbidity would be valuable. Although there are some small trials of treatments with dual gut–brain action, combination therapy, or integrated care, which include a proportion of individuals with IBS and any mental disorder comorbidity (ie, anxiety, depression, and somatic symptom disorders, either alone or combined),[80] large scale studies could facilitate better understanding of IBS–mental health transdiagnostic processes.

Self-administered assessment tools for symptoms of mental disorders that have been validated in IBS populations are needed. Validation tools will facilitate precise profiling of anxiety and depressive symptoms in IBS, allow changes in response to treatment to be measured, and provide accurate cutoff points for case identification, which have been shown to differ in patients with inflammatory bowel disease compared with the general population, for example.[81] The development and validation of combined gut–brain symptom assessment tools might also be possible.

The utility of measuring symptom-specific anxiety, in addition to general anxiety, in treatment trials requires evaluation, given recent evidence questioning its role as a driver of general anxiety or symptom severity in IBS.[82] Evaluation of whether central modulators or psychological interventions can reduce symptom-specific anxiety and somatic symptoms is needed.

Conclusion

Despite the high prevalence of common mental disorder comorbidity, and the detrimental effect on health-care service use, functioning, and quality of life, little attention has been paid to psychological comorbidity in previous RCTs of IBS. Trials run by multidisciplinary research teams that consider common mental disorder comorbidity in their design, implementation, and analysis are required to expose true treatment effects, in patients with IBS alone and in patients with concurrent common mental disorders. Measurement of psychological symptoms via validated tools should become routine practice, whether centrally driven or not. These data might then also be synthesised for better understanding of treatment efficacy. Reporting the temporal sequence of the onset of gastrointestinal and psychological symptoms will improve patient phenotyping, and stratified randomisation based on this could also provide some insight into treatment mechanisms of action. High quality RCTs of treatments with dual gut–brain action (such as neuromodulators), psychotherapeutic, integrated care, and microbiome-targeted approaches are also required to bridge the research gaps and, ultimately, to deliver more personalised care for individuals with IBS.

Contributors

HMS developed the concept. All authors drafted and critically reviewed the Viewpoint.

Declaration of interests

HMS and ACF declare no competing interests. Outside of the present work, AM-W served as an invited speaker at inflammatory bowel disease-related conferences co-organised by Crohn's & Colitis Australia (a charity), Janssen, and Ferring Pharmaceuticals, and received a speaker's fee.

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