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TITLE PAGE

Title: Personalisation of Therapy in Irritable Bowel Syndrome: A Hypothesis.

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Abbreviations:

5-HT	5-hydroxytryptamine
BDA	British Dietetic Association
BSFS	Bristol stool form scale
CBT	cognitive behavioural therapy
DGBI	disorder of gut-brain interaction
FC	functional constipation
FDA	Food and Drug Administration
FODMAP	fermentable oligosaccharides, disaccharides, monosaccharides, and polyols
HADS	hospital anxiety and depression scale
IBS	irritable bowel syndrome
IBS-C	IBS with constipation
IBS-D	IBS with diarrhoea

IBS-M	IBS with mixed bowel habits
IBS-U	IBS unclassified
IBS-SSS	IBS severity scoring system
LCA	latent class analysis
MDCP	multi-dimensional clinical profile
NICE	National Institute for Health and Care Excellence
RCT	randomised controlled trial
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitors
TCA	tricyclic antidepressant

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ABSTRACT

Irritable bowel syndrome (IBS) is a common disorder of gut-brain interaction characterised by symptoms of abdominal pain, occurring at least 1 day per week, and a change in stool frequency or form. Conventionally, patients with IBS are subtyped according to their predominant bowel habit and this is used to direct symptom-based treatment. However, this approach is probably an over-simplification of what is recognised to be a complex, multi-dimensional condition and other factors, such as psychological health, are known to influence symptom severity and prognosis. We have previously used latent class analysis, a method of mathematical modelling, to demonstrate that people with IBS can be classified into seven unique clusters based on a combination of gastrointestinal symptoms, abdominal pain, extra-intestinal symptoms, and psychological co-morbidity. The clusters predict prognosis of IBS, in terms of symptom severity, healthcare utilisation, in terms of consultation behaviour, prescribing, and costs, and impact, in terms of quality of life, work and productivity, activities of daily living, and income. We propose that these clusters could be used to direct IBS treatment in a more personalised way that better recognises the heterogenous nature of the condition and explore this hypothesis in detail in this review. First, we present new data providing additional validation of our seven-cluster model. Second, we conduct a comprehensive evidence-based review of the management of IBS encompassing general measures, including patient education, lifestyle, and diet; treatment of diarrhoea; treatment of constipation; treatment of abdominal pain; and treatment of co-existent psychological symptoms. Third, based on this evidence, we propose a framework of first- and second-line treatments according to IBS cluster. Finally, we discuss what further research is needed to implement this approach in clinical practice, including the need for randomised trials comparing cluster-based treatment with conventional treatment according to stool subtype.

INTRODUCTION

Irritable bowel syndrome (IBS) is a common disorder of gut-brain interaction (DGBI),(1) estimated to affect between 5% and 10% of the global population at any one time.(2) Characterised by chronic gastrointestinal symptoms, in particular abdominal pain and altered bowel habit, which are frequently debilitating in their severity, the impact of IBS on those suffering from the condition is considerable. IBS also places a substantial burden on healthcare services and budgets. In the UK, a recent analysis concluded that IBS treatment and care cost almost £2 billion per annum,(3) and other countries, such as Germany, China, and the USA have reported that the economic toll of IBS is similarly high.(4-6) IBS has a negative impact on health-related quality of life, comparable with other chronic diseases, such as heart failure or chronic lung disease.(7) People with IBS often report a loss of freedom and spontaneity, due to the severity and unpredictability of their symptoms,(8) and identify that IBS affects their ability to socialise, form close relationships, travel, and work effectively.(9) Almost 30% of people with IBS have needed to take time off work due to their symptoms, with between 72 and 188 million hours of work lost due to IBS per year in the UK among those of working age.(10) In addition, over 80% of those with IBS report either overall work impairment due to their symptoms or that they have attended their workplace despite not feeling well enough to be there.(10) Unfortunately, the effects of IBS on a person's life are often hidden and may be difficult for others to understand, meaning that patients can feel stigmatised by family, friends, and healthcare professionals.(11) Perhaps unsurprisingly, therefore, people with IBS are willing to tolerate considerable theoretical risks to be free of their symptoms. In one study,(12) patients would accept a median 2% risk of death for a 98% chance of permanent cure and, in another study, they were willing to give up 25% of their remaining life expectancy, an average of 15 years, to be symptom-free.(13)

A diagnosis of IBS is made using the Rome criteria, which were last updated in 2016.(14) This current iteration, Rome IV, defines IBS as the presence of abdominal pain, at a frequency of at least 1 day per week, associated with a change in stool frequency or form. Patients are subtyped according to their predominant bowel habit into one of four categories, which are used to direct treatment: IBS with diarrhoea (IBS-D), IBS with constipation (IBS-C), IBS with mixed bowel habits (IBS-M), if they experience diarrhoea and constipation equally often, or IBS unclassified (IBS-U), if they do not meet criteria for the other three subtypes (Figure 1). Predominant bowel habit is defined according to the proportion of stools that are loose or hard, using the Bristol stool form scale (BSFS), on days when the stools are abnormal. Randomised controlled trials (RCTs) in patients with IBS-D or IBS-C use endpoints that define treatment response clearly and, accordingly, these subtypes have been a focus for new drug development over many years.(15, 16) However, consensus on endpoints for IBS-M or IBS-U is lacking, and defining them may be challenging. Consequently, patients in these subtypes, who account for between 40% and 50% of people with IBS,(2) are left disenfranchised by the current system when it comes to both participation in RCTs and access to novel treatment options.

Another problem with the current classification of IBS is that it places the emphasis entirely on gastrointestinal symptoms, despite IBS being a complex, heterogenous disorder. The gut-brain axis, the two-way communication system between the gastrointestinal tract and the central nervous system, is key to our current conceptualisation of IBS.(17) It is well-established that psychological health can influence the development of IBS and the experience of gastrointestinal symptoms, but also that the converse is equally true.(18, 19) Moreover, clear risk factors for developing IBS, such as an history of enteric infection,(20) are recognised, and the pathophysiology of IBS, although not understood completely, is complex, with multiple factors, such as genetics, the microbiome, immune function, and

visceral hypersensitivity, all being proposed as underlying mechanisms.(21) However, the relative influence of any particular factor will vary for any individual person with IBS.

In acknowledgement of these complexities, the Rome Foundation have published the multi-dimensional clinical profile (MDCP).(22) This is a framework encouraging clinicians to evaluate factors other than gastrointestinal symptoms when assessing a patient with IBS, including psychological health, using this information to formulate a more personalised management plan. However, the MDCP approach is limited by the fact that, beyond physicians with a specialist interest in DGBI, it is relatively unknown, and stops short of recommending the systematic inclusion of these factors in the general diagnosis and subgrouping of people with IBS. This means that most patients with IBS will derive no benefit from the proposals it makes.

There has been increasing interest in new approaches for subgrouping people with IBS that include psychological health data routinely, using a technique called latent class analysis (LCA).(23, 24) LCA is a form of mathematical modelling that identifies previously unobserved clusters within multivariate data. The variables for inclusion in the model are pre-defined and LCA is then applied to determine the optimum solution for grouping participants into clusters, based on these variables, measured using statistical tests of model fit. We have previously applied this technique to a large cohort of individuals with Rome III and Rome IV IBS.(25) We have shown that people can be classified into seven distinct clusters based on their pattern of bowel symptoms and abdominal pain, and levels of psychological co-morbidity, based on degree of extra-intestinal symptom reporting and anxiety and depression scores (Figure 2). These seven clusters were reproducible irrespective of whether IBS was defined according to Rome III or Rome IV criteria. Other researchers have also used LCA to classify IBS and, although the precise characteristics and number of clusters vary between

studies, there is broad agreement that cluster separation occurs based on a combination of gastrointestinal and psychological symptoms.(23, 24, 26, 27)

Follow-up of our model at 12-months showed that most people in a cluster with high levels of psychological co-morbidity at baseline remained in such a cluster at follow-up and *vice versa*.(28) Individuals in a cluster with a high psychological burden at baseline had more severe IBS symptoms at follow-up, which had a greater impact on activities of daily living, compared with those in a cluster with a low psychological burden. They also received a higher mean number of treatments for their IBS and were more likely to have seen a doctor about their symptoms over the preceding 12 months.

We applied our model to another cohort of people with IBS, subsequently, to assess its correlation with the impact of IBS.(29) Individuals in the four clusters with the highest psychological burden, and particularly those in cluster 6 with the highest overall gastrointestinal symptom levels and highest psychological burden, had reductions in IBS-specific and general quality of life, and ability to work, engage in social and leisure activities, and maintain close relationships, and their annual income was also impacted. Healthcare costs associated with IBS were also highest in these four clusters. More recently, we examined the applicability of the clusters in the Rome Foundation global epidemiological survey, containing over 2000 individuals with Rome IV-defined IBS recruited from a community setting in 26 different countries.(30) All seven clusters were reproducible and, again, those in clusters with the highest psychological burden, and particularly cluster 6, exhibited higher levels of healthcare-seeking, and had higher symptom severity and lower quality of life.(31) In this study, the clusters with highest psychological burden were also more likely to have undergone previous abdominal surgery.

We have sought to further refine our understanding of the seven-cluster model by presenting additional analyses from our original study (Table 1).(25) Although measures of

abdominal pain, anxiety and depression scores, and extra-intestinal symptom reporting were included in model derivation, we have now cross-tabulated these variables by cluster to provide additional validation of the cluster descriptions. This shows that those clusters characterised by high psychological burden had a higher prevalence of abnormal anxiety and depression scores, assessed using the hospital anxiety and depression scale (HADS), and higher levels of somatoform symptom reporting, assessed via the patient health questionnaire-12. Other measures of psychological health, including gastrointestinal-symptom specific anxiety, assessed using the visceral sensitivity index, and perceived stress, assessed via the Cohen perceived stress scale, showed a similar association, with higher scores in those clusters defined by high psychological burden. The proportion of people reporting daily abdominal pain and severe symptoms, based on the IBS symptom severity score was also higher in these clusters. These clusters were also characterised by either high levels of abdominal pain alone or high overall gastrointestinal symptoms, in addition to the high psychological burden. Lastly, we examined the distribution of IBS subtypes according to cluster. Most people in constipation-defined clusters 5 and 7 met criteria for IBS-C, with very few having IBS-M or IBS-D, whereas in diarrhoea-defined clusters 1 and 4, most people had IBS-D or IBS-M. In clusters 2, 3, and 6 with low overall bowel symptoms but high levels of abdominal pain, low overall gastrointestinal symptom severity, or high overall gastrointestinal symptom severity, respectively, all subtypes were represented, but most people met criteria for IBS-M.

Based on the findings of our group, and others, we propose augmentation of the traditional paradigm of IBS subtyping using a patient's predominant bowel habit with the addition of a third axis representing levels of abdominal pain, extra-intestinal symptom reporting, and psychological burden. This transforms our perspective of IBS into one with three dimensions and it is possible to represent all seven of our clusters in this diagram,

(Figure 3). Viewed in this way, we can conceptualise that, not only should we be targeting treatment at a patient's predominant bowel habit, but we should also be considering their overall symptom burden, including their experience of abdominal pain, and their psychological health. Using the clusters to direct therapy could unlock an approach which delivers integrated and, ultimately, more personalised care, but in a standardised way. This has the potential to benefit the most patients with IBS. Making an early positive diagnosis of IBS, based on typical symptoms alongside limited investigations, to facilitate early initiation of an efficacious treatment is key to the successful management of the condition.(32) Having the ability to target combinations of treatments more effectively could, therefore, change the natural history of the disorder and improve outcomes. However, it is vital that any such approach be underpinned by evidence-based principles. The remainder of this article will, therefore, review the evidence for the management of IBS according to both gastrointestinal and psychological symptoms, discussing how this could be applied to the subgrouping model we have proposed, and consider what further research is needed to test our hypothesis of personalised, cluster-based, treatment in clinical practice.

Search strategy and selection criteria

We searched MEDLINE from 1st January 1947 to 30th June 2024 to identify references for this viewpoint. Search terms included "*irritable bowel syndrome* or *functional diseases*, *colon*" combined with the following: "*education*, *sleep*, *lifestyle*, *exercise*, *probiotics*, *fructan*, *FODMAP*, *fructooligosaccharide*, *dietary fibre*, *psyllium*, *parasympatholytics*, *scopolamine derivatives*, *trimebutine*, *muscarinic antagonists*, *menthol*, *menthol*, *piperita*, *alosetron, eluxadoline, ramosetron, rifaximin*, *lubiprostone*, *linaclotide, plecanatide, tenapanor*, *psychotropic drugs*, *antidepressive agents*, *desipramine*, *imipramine*,

trimipramine, *doxepin, dothiepin, nortriptyline*, *amitriptyline*, *serotonin uptake inhibitors*, *paroxetine, sertraline, fluoxetine, citalopram*, *pregabalin*, *gabapentin*, *duloxetine*, *therapy*, *psychotherapy*, *behaviour therapy*, *relaxation therapy*, or *hypnosis*." Those most relevant to the hypothesis presented in this article were prioritised. We selected meta-analyses and RCTs preferentially and, therefore, the best available evidence was used to inform the article. Where there were no studies available to support the approaches suggested in the article, we relied on our clinical experience in this field.

MANAGEMENT OF IBS

General first-line approaches

Education

Good communication is a key tenet of IBS management.(33) It is important that patients have a clear understanding of how gastrointestinal symptoms can arise in the absence of organic pathology, with explanation framed in terms of the gut-brain axis and, therefore, why investigations may be normal. Discussion should manage expectations appropriately, emphasising that treatment aims to improve symptoms and lessen their impact, but that complete cure is rarely achievable.(34, 35) One RCT compared the effects of structured patient group education on patient knowledge, symptoms, and quality of life,(36) with receiving only written information about IBS. Education was delivered by a range of healthcare professionals, including nurses, gastroenterologists, dietitians, physiotherapists, and psychologists. Patient group education resulted in greater reductions in IBS symptom severity and gastrointestinal symptom-specific anxiety and led to significant improvements in several aspects of health-related quality of life. In another study examining the impact of a one-off multidisciplinary education class for IBS in 344 patients,(37) class attendees showed greater improvements in symptoms and health-promoting behaviours compared with non-attendees at 6-month follow-up. However, there was no effect on quality of life, patient satisfaction, or healthcare utilisation. Finally, Labus *et al.* randomised patients with IBS to receive a brief psycho-educational intervention or waiting list control.(38) The intervention emphasised the mind-body connection in IBS, promoted self-help strategies, and provided information on relaxation techniques. Patients receiving education showed greater improvements in symptom severity, gastrointestinal symptom-specific anxiety, depression,

and quality of life, and many of these changes were sustained at 3-month follow-up. Overall, therefore, providing patients with good quality education about IBS is likely to be beneficial. The success of single-session group education offers a practical and sustainable way to deliver this intervention in clinical practice. There is also evidence to suggest education can be provided successfully by digital means, such as webinars.(39)

Exercise

Exercise is important for maintaining good physical and mental health.(40-42) It can also accelerate gastrointestinal transit and improve intestinal gas clearance,(43, 44) and might, therefore, be beneficial for some patients with IBS. One trial compared 12 weeks of an exercise intervention with usual care.(45) In total, 305 patients with IBS were invited to participate, although only 56 (18%) agreed. Those in the exercise group reported significant improvements in constipation, compared with those assigned to usual care, but there were no differences between groups for other IBS symptoms or quality of life. Another study randomised 102 patients with IBS to receive a physical exercise programme or usual care for 12 weeks, 75 (74%) of whom completed the study.(46) Physical exercise resulted in significantly greater improvements in IBS symptom severity scores, compared with usual care, and these positive effects persisted in 39 patients followed up for a median of 5.2 years.(47) A recent Cochrane review examined data from 11 RCTs,(48) including the two aforementioned studies. The authors concluded that exercise, including yoga, treadmill exercise, or support to increase physical activity may improve global symptoms in IBS, but not abdominal pain or quality of life. However, confidence in these conclusions was limited due to the very low quality of available evidence. Nevertheless, it seems reasonable to encourage patients with IBS to increase their physical activity, if possible, due to the potential for positive changes in gastrointestinal symptoms, as well as other general health benefits.

Lifestyle advice

Patients with IBS often report greater psychological stress than controls,(49) and there is a recognised relationship between stress and gastrointestinal symptoms in IBS,(50) although this may be reciprocal rather than causal. However, although findings are inconsistent, studies have shown that stress can alter gastrointestinal motility and intestinal permeability, influence visceral sensitivity and perception, and affect the activity of the autonomic nervous system.(51, 52) All of these are mechanisms by which stress could trigger gastrointestinal symptoms. A systematic review of stress management techniques in IBS concluded that these may result in short-term reductions in bowel symptoms and improve mental health, but whether there were longer term benefits was unclear.(53) Despite this, it seems reasonable, as recommended by previous management guidelines,(54) to encourage relaxation and promote leisure time among patients with IBS, some of whom may derive benefit.

Sleep disturbance is commonly reported in IBS.(55) In a large population-based survey of over 2000 individuals, when adjusted for age and sex, sleep disturbance was reported by 13.5% of participants, of whom one-third met criteria for IBS.(56) Following adjustment for age, sex, and somatisation scores, IBS was significantly more common among people with sleep disturbance. A recent study examined the effects of subjective sleep disturbance, assessed using the Pittsburgh Sleep Quality Index, and objective sleep disturbance, using wrist-worn actigraphy, in patients with IBS.(57) This showed that patient perception of sleep was the most important factor affecting gastrointestinal symptom reporting. Poor subjective sleep quality was associated with higher levels of gastrointestinal symptoms being experienced the following day, whereas there was no association between symptoms and objective measures of sleep quality. In cross-lagged analysis, gastrointestinal symptoms were not the cause of poor sleep quality. Another study reported that the

relationship between poor sleep and IBS symptoms cannot be explained by psychological factors.(58) However, irrespective of these uncertainties, asking patients with IBS about their sleep quality and offering interventions, such as sleep hygiene advice, to try to improve sleep might be helpful for improving gastrointestinal symptoms, although studies of this approach in IBS are needed.

Dietary fibre supplementation

Fibre may be insoluble, such as bran, or soluble, such as ispaghula. Insoluble fibre adds bulk to the intestinal contents and increases stool water content, which can accelerate gut transit time.(59) Soluble fibre forms a gel with water and is digested by gut bacteria, a process that produces metabolites, such as short-chain fatty acids or secondary bile acids,(60) which can influence gut function and stimulate transit via their interaction with enteric nerves and intestinal smooth muscle.(61) These metabolites may also have anti-inflammatory effects.(61) A previous systematic review and meta-analysis of 14 RCTs showed a significant benefit of fibre supplementation over placebo for global IBS symptoms.(62) Subgroup analysis showed that the benefit was confined to studies of ispaghula, with no evidence that bran was efficacious. Side-effects, such as pain, bloating, or flatulence, are common with fibre supplements, and perhaps more so with insoluble preparations.(63) However, whether there is a difference in the adverse event profile of soluble and insoluble fibre could not be discerned in the meta-analysis due to insufficient reporting of data. Fibre is often recommended as a treatment for constipation, which, given its effects on stool form and frequency, is perhaps unsurprising, although this approach has not been the subject of rigorous clinical trials.(64) Nevertheless, as a simple, inexpensive, and safe treatment, it seems reasonable to recommend soluble fibre supplements to patients with IBS.

Probiotics

Probiotics are live micro-organisms that when administered in adequate amounts confer a benefit on the host.(65) Given the possible role of the gut microbiome in IBS, there have been multiple RCTs of probiotics in IBS, summarised in a recent meta-analysis.(66) However, the certainty in the evidence for their efficacy is low due to shortcomings in the design of many of the trials and, despite data being pooled from 82 separate placebo-controlled trials in the aforementioned analysis,(66) there appears to be no consistent effect of a particular strain or species of probiotic on individual symptoms of IBS. However, there was evidence of efficacy for some *Lactobacillus* and *Bifidobacteria* strains, as well as some combinations of various probiotics, and it seems reasonable to make informal recommendations to patients based on this meta-analysis and the individual trial results.

Dietary advice

Standard first-line dietary advice for IBS from the British Dietetic Association (BDA), and approved by the National Institute of Health and Care Excellence (NICE), consists of recommendations concerning general eating patterns and dietary constituents.(67) This includes advice to consume small regular meals, avoid skipping meals or eating late at night, and reduce caffeine, fizzy drinks, rich or fatty food, and fresh fruit intake. BDA/NICE dietary advice is often used as a comparator in trials of dietary interventions.(68) However, as it has never been used as an active intervention itself in an RCT, it is difficult to make direct inferences about its efficacy. In a network meta-analysis of 13 trials,(68) of which five used the BDA/NICE diet as the comparator, it ranked second for improvement in global symptoms of IBS after indirect comparison, behind a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs), although it was not superior to any of the other dietary interventions studied. It ranked lower in terms of its impact on

abdominal pain, bloating, or improvement in bowel habit, and again was not superior to any of the other interventions. A smartphone application-delivered FODMAP-lowering diet has also been tested as a treatment for IBS in primary care in a large Belgian RCT.(69) This is less complex to follow than a true low FODMAP diet and, therefore, more feasible to deliver in such a setting. It was superior to the antispasmodic otilonium, irrespective of stool subtype.

Treating constipation and bloating

Laxatives are recommended as first-line treatment for IBS-C.(34) However, aside from two placebo-controlled trials of polyethylene glycol in IBS,(70, 71) only one of which reported an increase in stool frequency,(70) evidence for benefit is limited. Nevertheless, they have been shown to be more efficacious than placebo for constipation more generally, based on the results of studies in functional constipation (FC).(72) Although this is defined as a separate DGBI to IBS-C,(14) symptoms are broadly similar between the two disorders,(73) with the exception of abdominal pain, which is experienced more frequently in IBS-C. These clinical similarities, together with the fact that laxatives are inexpensive and safe, provides a good rationale for using laxatives first-line to treat constipation in IBS.

In cases where this approach is ineffective, other drugs have been developed. 5-hydoxytryptamine-4 receptor (5-HT_4) agonists, such as tegaserod, increase gastrointestinal motility.(74) Tegaserod was approved in the USA for the short-term treatment of IBS-C in women and for treating FC in women and men but was withdrawn in 2007 due to concerns about an increased risk of cardiovascular and cerebrovascular ischaemic events.(75) However, subsequent observational data found no association with an increased risk of these events and so, in 2019, tegaserod was reintroduced in the USA, but only for treating IBS in women under 65 years of age with no history of cardiovascular ischaemia. It has now been withdrawn again for commercial reasons and remains unavailable outside the USA.

Prucalopride, another 5-HT_4 receptor agonist, is widely available, has a good safety profile and is efficacious for FC,(72) compared with placebo, but has not been evaluated in RCTs in IBS-C. Despite this, based on the same rationale discussed above with respect to laxative treatment, it may be reasonable to extrapolate stool consistency data from trials of prucalopride in FC to justify using the drug to treat constipation in IBS.

A second-line option for when laxatives fail to provide adequate relief are secretagogue drugs, such as linaclotide, plecanatide, or tenapanor. These drugs activate ion channels in the epithelium of the intestinal mucosa causing an influx of electrolytes and water into the lumen, softening stools and increasing gastrointestinal transit. Linaclotide and plecanatide stimulate the guanylate cyclase-C receptor, whereas tenapanor inhibits the gastrointestinal sodium-hydrogen exchanger-3. All have been shown to be superior to placebo in RCTs.(76-78) The main adverse event reported for all three drugs is diarrhoea. No head-to-head trials of these drugs have been conducted. However, because all have been compared with a placebo in existing RCTs, a network meta-analysis was able to compare them indirectly to determine their relative efficacy.(79) This used the Food and Drug Administration (FDA) endpoint for improvement in stool frequency in trials in IBS-C, which consists of an increase of ≥1 complete spontaneous bowel movement per week over baseline.(15) Linaclotide 290µg daily, plecanatide 6mg daily, and tenapanor 50mg daily were all more efficacious than placebo for this endpoint, but linaclotide 290µg daily ranked first, suggesting that this is likely to be the most efficacious option. Their effects on bloating in patients with IBS-C has been assessed, specifically, in another network meta-analysis of placebo-controlled trials, which also included data from RCTs of tegaserod.(80) All drugs were superior to placebo for the symptom of bloating, but again linaclotide 290µg daily ranked first.

Treating diarrhoea and urgency

First-line treatment of diarrhoea is usually with loperamide,(34) although evidence for its efficacy in IBS is lacking as only two small trials have been conducted, involving a total of 42 patients with IBS-D or IBS-M.(81, 82) A pooled analysis of data from these trials showed no benefit of loperamide on global IBS symptoms compared with placebo.(83) However, both trials demonstrated improvements in stool frequency and consistency. Loperamide is, therefore, a reasonable first-choice drug for diarrhoea in IBS, although patients often report inadequate relief of their symptoms.(84)

Enterosgel is an intestinal adsorbent. It is classed as a medical device, as it has no pharmacological action, and is available over the counter. It reduces the duration of an acute diarrhoeal illness significantly,(85) and is thought to exert its effects by binding bile acids, bacterial products, and other potentially noxious substances in the gastrointestinal tract. In a large RCT conducted in the UK,(86) it was more efficacious than placebo in terms of the FDA endpoint for stool consistency in IBS-D, which consists of a BSFS stool of <5 on ≥50% of days.(15) It also improved urgency scores significantly compared with placebo.

A low FODMAP diet has also been assessed as a treatment for diarrhoea, specifically, in IBS. A network meta-analysis identified six RCTs comparing a low FODMAP diet with a variety of control interventions,(68) recruiting only patients with IBS-D, which were pooled using an endpoint of a 30% improvement in bowel habit on the IBS-SSS. Although a low FODMAP diet ranked first, it was not superior to sham dietary advice, and there was also no significant difference in efficacy compared with BDA/NICE dietary advice. Its effect on urgency was reported in one RCT, where it was more effective than BDA/NICE dietary advice.(87)

Tricyclic antidepressants (TCAs) are often used at low doses in IBS, for the treatment of abdominal pain and global symptoms. However, due to their anti-cholinergic effects, they

can have peripheral effects on the gut including slowing gastrointestinal motility.(88, 89) In this context, they are acting as gut-brain neuromodulators.(90) A previous RCT examined the effects of amitriptyline 10mg daily compared with placebo in 54 patients with Rome II IBS-D.(91) Following 2 months of treatment, those receiving amitriptyline reported a significantly greater reduction in frequency of loose stools compared with placebo, but no data on its effect on urgency were reported.

Other drugs have been developing specifically for treating IBS-D. These include rifaximin, eluxadoline, alosetron, and ramosetron. Rifaximin is a minimally absorbed antibiotic that is postulated to work in IBS via mechanisms related to limited changes in the faecal microbiome,(92, 93) although these effects are perhaps too modest to explain any benefit of the drug,(94) and because some studies demonstrate an overlap between IBS and small intestinal bacterial overgrowth, albeit based on largely low-quality evidence.(95) Eluxadoline is a mixed opioid receptor drug. Similar to loperamide, eluxadoline activates intestinal μ-opioid receptors, thereby slowing gastrointestinal motility and reducing diarrhoea, but also acts on δ-opioid receptors modulating pain. Alosetron and ramosetron are 5-HT_3 antagonists that slow gastrointestinal motility. All these drugs have been tested in placebo-controlled trials and are efficacious in IBS-D. (74, 96-98) Again, a network meta-analysis has been conducted examining their relative efficacy in terms of the FDA endpoint for improvement in stool consistency in trials in IBS-D.(99) In this analysis, all drugs were superior to placebo, although none were superior to any other drug on indirect comparison. Alosetron 1mg twice daily and ramosetron 5μg once daily ranked first and second, respectively. Individual placebo-controlled trials have demonstrated that all these drugs have beneficial effects on urgency in patients with IBS-D.(97, 98, 100, 101)

Eluxadoline has been associated with serious side effects, including pancreatitis and sphincter of Oddi spasm,(102) and is not widely available. Alosetron was originally licensed

for the treatment of women with IBS-D. Due to safety concerns relating to severe constipation and ischaemic colitis, it was withdrawn,(103) but has since been reintroduced at a lower dose of 0.5mg twice daily for severe IBS-D in women. Observational data shows that alosetron is safe and efficacious at this dose among this patient demographic,(104) but it remains unavailable outside the USA. Ramosetron is only available in Japan and some other Asian countries. However, ondansetron, another 5-HT_3 antagonist, is widely available, licensed for the treatment of chemotherapy-induced nausea and vomiting, and has a good safety record. A meta-analysis of three RCTs demonstrated that ondansetron was superior to placebo for the FDA stool consistency endpoint in IBS-D and for a ≥30% improvement in urgency scores.(105) Consequently, these data suggest a class effect of 5-HT_3 antagonists for treating diarrhoea and urgency in IBS. The role of ondansetron should, therefore, be explored further in larger trials, given its wider availability. Irrespective of this, it could already be considered as a treatment option, given the limited availability of drugs for these debilitating symptoms.

Treating abdominal pain

First-line treatment of abdominal pain in IBS consists of antispasmodic drugs, such as hyoscine, otilonium, or alverine, or peppermint oil.(34) The latter has not only antispasmodic effects due to its active ingredient, L-menthol, which relaxes gastrointestinal smooth muscle,(106) but also analgesic effects, via transient receptor potential channels.(107) In a network meta-analysis,(108) containing 10 placebo-controlled trials, antispasmodic drugs as a class were more efficacious than placebo for abdominal pain, and ranked second for this endpoint, behind TCAs. However, many of these RCTs were over 20 years old and used historical definitions of IBS, as well as outdated endpoints to judge efficacy, and there were a variety of drugs used and heterogeneity between trials. The efficacy of peppermint oil for

abdominal pain in IBS was studied in a recently updated meta-analysis.(109) Overall, in seven trials, there was a benefit of peppermint oil over placebo, but this was modest, and the two most recent trials,(110, 111) which used more stringent endpoints, did not demonstrate superiority of peppermint oil.

Trials of licensed drugs for both IBS-C and IBS-D use FDA-recommended composite endpoints to judge efficacy that include a combination of either the stool frequency or stool consistency endpoint together with a ≥30% improvement in abdominal pain severity.(15) These trials also report efficacy in terms of a ≥30% improvement in abdominal pain severity as a separate endpoint. This, therefore, makes it possible to examine their effects on abdominal pain alone in both IBS-C and IBS-D. In IBS-C, a network meta-analysis examined the relative efficacy of secretagogues for the FDA endpoint for abdominal pain.(79) In this analysis, linaclotide 290µg, tenapanor 50mg, and plecanatide 3mg or 6mg once daily were all superior to placebo, but linaclotide 290µg ranked first, followed by tenapanor 50mg.

In IBS-D, again in a network meta-analysis,(99) ramosetron 2.5µg or 5µg once daily, alosetron 1mg twice daily, and eluxadoline 100mg twice daily were all more efficacious than placebo for the FDA endpoint for abdominal pain, but rifaximin 550mg three times daily for 2 weeks and eluxadoline 75mg twice daily did not demonstrate any benefit. Ramosetron 2.5µg and 5µg once daily were ranked first and second, respectively, on indirect comparison, with alosetron 1mg twice daily third. In a meta-analysis of three RCTs of ondansetron versus placebo there was no benefit of active drug for the FDA abdominal pain endpoint,(105) suggesting it is best used in patients with diarrhoea and urgency where pain is less of an issue.

TCAs can reduce visceral hypersensitivity,(112) via effects related to alterations in central pain processing and perception. In a meta-analysis of RCTs of gut-brain neuromodulators, four trials reported the effect of TCAs on abdominal pain.(113) Overall,

TCAs were more efficacious than placebo and, in a network meta-analysis that also included trials of soluble fibre, antispasmodics, and peppermint oil, TCAs ranked first for this endpoint.(108) However, there were only 184 patients included in these four trials and endpoints used were less stringent than those currently recommended in IBS treatment trials. A recent RCT of low-dose amitriptyline, titrated from 10mg daily to a maximum of 30mg daily, versus placebo, in 463 patients with IBS demonstrated amitriptyline was superior to placebo in terms of a ≥30% improvement in abdominal pain severity at 6 months.(114)

Evidence for the efficacy of other gut-brain neuromodulators for treating abdominal pain in IBS is limited. In the aforementioned meta-analysis of trials of gut-brain neuromodulators,(113) there was no benefit of selective serotonin reuptake inhibitors (SSRIs) over placebo for abdominal pain in three RCTs, although these only recruited 167 patients and the two trials of fluoxetine demonstrated efficacy when considered separately.(115, 116) In a small RCT of venlafaxine, a serotonin norepinephrine reuptake inhibitor (SNRI), the drug was superior to placebo in 30 patients with IBS, in terms of abdominal pain frequency scores at 12 weeks.(117) It seemed to improve abdominal pain irrespective of whether stool frequency increased or decreased at the onset of pain. However, duloxetine has more potent effects on norepinephrine transporters than venlafaxine,(118) and larger doses of venlafaxine are required to have analgesic effects.(119) There is some evidence for efficacy of duloxetine for abdominal pain in IBS in small placebo-controlled trials,(120, 121) and for efficacy for treating pain in other chronic disorders, such as fibromyalgia and low back pain, in meta-analyses and RCTs.(122-124)

Brain-gut behavioural treatments are also suggested as a potential treatment for abdominal pain in IBS in some management guidelines.(125) However, until recently there was little evidence for this. In a recent network meta-analysis of 42 RCTs,(126) brain-gut behavioural treatments with the largest numbers of trials and patients recruited and with

evidence for efficacy for abdominal pain included self-guided or minimal contact cognitive behavioural therapy (CBT), face-to-face multicomponent behavioural therapy, and face-to-face gut-directed hypnotherapy. These were all superior to a waiting list control intervention, although no brain-gut behavioural treatment was superior to another. In addition, digital gut-directed hypnotherapy and digital relaxation therapy were superior to several control interventions including treatment as usual, education and/or support, and waiting list control and ranked first and second in the network meta-analysis, respectively, although these were studied in only one or two trials.

For severe or refractory pain, the use of combinations of gut-brain neuromodulators, termed augmentation, has been suggested.(90) Combinations of neuropathic analgesics (e.g., duloxetine plus gabapentin) were more efficacious than monotherapy in a large cohort of patients with severe chronic continuous abdominal pain.(127) Attention to the potential for development of the serotonin syndrome is required for some combinations, especially those involving both SSRIs and SNRIs.

Treating psychological symptoms

Psychological symptoms often co-exist with gastrointestinal symptoms in IBS and may be the primary concern for some patients. However, it is important, when assessing patients, to distinguish between psychological symptoms related to the gut-brain axis, for example, gastrointestinal symptom-specific anxiety or the psychological consequences of the impact of symptoms on daily functioning, and a co-existing common mental disorder, such as anxiety or depression, because this could affect therapeutic approaches.(128) Gut-brain neuromodulators, which, as discussed, are often used to treat gastrointestinal symptoms in IBS, are primarily antidepressants, and both TCAs and SSRIs are efficacious in this context.(113)

TCAs are generally used at low doses in IBS, which would be considered subtherapeutic for the treatment of depression or anxiety. Indeed, in the recent RCT of low-dose amitriptyline, although when titrated from 10mg daily to a maximum of 30mg daily the drug improved global IBS symptoms and abdominal pain significantly, compared with placebo, there was no effect on anxiety or depression scores.(114) This reinforces the idea that low-dose TCAs are acting on motility and sensation in IBS and, hence, may not be a good choice of gut-brain neuromodulator for patients with co-existing depression or anxiety, although higher doses have been used in other RCTs in IBS (e.g., up to 150mg daily of desipramine).(129)

An SSRI may be a better option, given these drugs are recommended first-line for the treatment of a common mental disorder in patients with other chronic health conditions by NICE.(130) However, specific evidence for the use of SSRIs in IBS patients with co-existing common mental disorders is lacking. In a previous study of citalopram 20mg once daily for IBS, there was a significant improvement in both gastrointestinal symptoms and anxiety and depression scores, compared with placebo at 6 weeks, although patients with a common mental disorder at baseline were excluded.(131) Improvements in gastrointestinal symptoms were independent of changes in mood scores. In contrast, in another study of fluoxetine 20mg once daily for IBS, which also excluded patients with depression at baseline, there was no improvement in psychological symptom scores versus placebo.(115) SNRIs are also licensed for the management of common mental disorders and there is some uncontrolled evidence that these can be particularly helpful for the management of IBS with co-existing psychological co-morbidity.(132)

CBT has been evaluated for the treatment of global symptoms in IBS,(113) and some trials also report its effects on anxiety and depression scores. The ACTIB study compared both telephone- and web-delivered CBT with treatment as usual for patients with IBS.(133)

At baseline, average anxiety scores, measured using the HADS, were abnormal in all three arms, although depression scores were normal. There were significant reductions in overall HADS scores for both telephone- and web-directed CBT, compared with treatment as usual, at 3-, 6-, and 12-month follow-up. These improvements were sustained at 24-month follow-up.(134) In two separate trials of gut-directed hypnotherapy conducted in Sweden, in which results for HADS scores were pooled, there was a greater decrease in HADS-anxiety scores with gut-directed hypnotherapy compared with control intervention, although this was not statistically significant, but no change in HADS-depression scores in either arm.(135) In another trial of group-delivered gut-directed hypnotherapy, there were significant differences seen in both HADS-anxiety and HADS-depression scores with active therapy versus a control of treatment as usual.(136) For patients with symptoms refractory to drugs and with co-existing psychological symptoms, a combination of a gut-brain neuromodulator and a brain-gut behavioural treatment may be more efficacious than monotherapy with either, as seen in depression and chronic headache.(137, 138)

Nevertheless, it is important to remember that although brain-gut behavioural treatments for IBS may improve symptoms of depression and anxiety, they are intended, primarily, to be brief gastrointestinal-symptom focused interventions.(128) Indeed, there is some evidence that global symptoms in patients with IBS and co-morbid anxiety or depression respond less well to brain-gut behavioural treatments.(139) Referral to a community-based general psychologist may, therefore, be required either prior to, or alongside, embarking on a brain-gut behavioural treatment that is intended specifically for IBS.(140)

For patients with both severe gastrointestinal symptoms and a high psychological burden, it is unlikely that a single intervention will be sufficient. In this situation, integrated multi-disciplinary care may be required. The evidence base for this is limited, although one

RCT reported superior outcomes for patients with DGBI with an integrated approach with gastroenterologists, dietitians, hypnotherapists, psychiatrists, and behavioural physiotherapists available in a single clinic, rather than seeing only a gastroenterologist.(141) In addition, in this study, the proportion of patients who classified their symptoms as severe or very severe at baseline who experienced symptom improvement was significantly higher in the multi-disciplinary clinic, compared with those who only saw a gastroenterologist.

Suggested approach to the treatment of IBS using the clusters

The clusters we describe are based on a mathematical formula and can be applied to any patient with IBS to enable classification into one of the clusters, if the gastrointestinal and psychological symptom variables we used to derive them are recorded by the patient (see appendix pages 1 to 3). Applying the evidence summarised above to the clusters we have described, and in order of the clusters in the model, the following approach for first- and second-line treatment could be considered, with the ultimate choice made after an informed discussion with the patient (Figure 4). Irrespective of cluster, education about the condition, within the context of the gut-brain axis, and lifestyle advice is required for all patients with IBS.

For cluster 1, where diarrhoea and urgency are the main symptoms, and the psychological burden is low, first-line treatment would be a choice of loperamide, ondansetron, or enterosgel as these have shown efficacy for diarrhoea and/or urgency, but perhaps less so for pain. Second-line options would include a low FODMAP diet, given its restrictive nature may not be suitable for all patients, a low-dose TCA, eluxadoline, or rifaximin, where the latter two are available.

For cluster 2, where bowel symptom severity is low but abdominal pain is dominant and the psychological burden is high, first-line therapy would be a choice of a low-dose TCA

or an SNRI, such as duloxetine, as these may be more likely to improve pain than an SSRI, and bowel habit is unlikely to be affected, with second-line treatment the consideration of adding in a brain-gut behavioural treatment.

For cluster 3, where both overall gastrointestinal symptom severity and the psychological burden are low, first-line treatment would be a choice of education, exercise, soluble fibre, probiotics, BDA/NICE dietary advice, or a FODMAP-lowered diet, rather than a true low FODMAP diet, given symptoms are generally mild and may respond to these measures alone. Second-line options would include laxatives, loperamide, or antispasmodics (including peppermint oil), depending on whether constipation, diarrhoea, or abdominal pain is the most troublesome symptom.

For cluster 4, where diarrhoea, abdominal pain, and urgency are the main symptoms and the psychological burden is high, first-line therapy would be a choice of alosetron or ramosetron, where available, or a low-dose TCA, as all have efficacy for both diarrhoea and pain, and alosetron and ramosetron have evidence of efficacy for urgency. Second-line treatment would include switching to, or adding in, eluxadoline or an SNRI. There could also be consideration given to addition of a brain-gut behavioural treatment.

For cluster 5, where constipation, abdominal pain, and bloating are the main symptoms and the psychological burden is high, first-line treatment would be a choice of one of the secretagogues, which all have efficacy for constipation, pain, and bloating. Second-line options would include adding in an SNRI, as this is unlikely to worsen bowel habit, or addition of a brain-gut behavioural treatment.

For cluster 6, where both overall gastrointestinal symptom severity and the psychological burden are high, first-line therapy might include augmentation using more than one gut-brain neuromodulator, but with consideration of multi-disciplinary level care from

the outset, given the severity of symptoms. Second-line treatment would include addition of a brain-gut behavioural treatment.

Lastly, for cluster 7, where constipation and bloating are the main symptoms, abdominal pain is less of an issue, and the psychological burden is low, first-line treatment would be a choice of a laxative or prucalopride, which both have efficacy for constipation and may be less likely to need to be discontinued due to diarrhoea, even though the evidence base for secretagogues for constipation and bloating in IBS-C is stronger. These could, therefore, be held in reserve as a second-line option to switch to, or add in.

FUTURE DIRECTIONS

In this article, we propose a novel subgrouping system for IBS and review the evidence for how it could be used to direct treatment. The clusters we describe are clinically intuitive and make the best use of available treatment, or combination of treatments, at the earliest possible opportunity with the aim of improving patient outcomes. This includes brain-gut behavioural treatments, which are often positioned third-line in IBS guidelines. We have demonstrated previously that these clusters exist in separate cohorts of people with IBS, including those living in the community. The clusters appear to predict not only disease burden but also outcomes during longitudinal follow-up. The clusters do fluctuate during follow-up,(28) although most people in a cluster with a high psychological burden at baseline will remain in one of the other clusters with a high psychological burden, even if their bowel symptoms fluctuate. If an individual patient does change cluster, then the treatment approach would then be that for the relevant new cluster. Nevertheless, further work is needed before this approach can be adopted in routine clinical practice. Although other investigators have demonstrated, using LCA, that people with IBS separate into clusters based on a combination

of gastrointestinal and psychological symptoms,(23, 24, 26, 27) independent replication of our clusters in other cohorts is required.

In addition, real-world studies demonstrating that efficacy of conventional treatment strategies for IBS, such as using a secretagogue for constipation, or a 5-HT_3 antagonist for diarrhoea, is impacted by cluster would be helpful in confirming our hypothesis that the use of drugs based on stool subtype alone is not the optimal approach to manage IBS. This is already supported, to some extent, by the observation that only 30% to 40% of patients will respond to a drug targeted at their predominant bowel habit in most RCTs conducted to date.(79, 99)

Finally, future trials are required that recruit unselected patients with IBS and randomise them to either conventional management, according to stool subtype, or a cluster-based approach, with therapy selected according to the suggestions we provide in this article, and where the impact on gastrointestinal symptoms, psychological symptoms, quality of life, and costs is compared between the two. Even if this were to be unsuccessful, we believe a new treatment paradigm for IBS is needed that is more inclusive, both in terms of allowing access to clinical research and novel therapies, and that considers the multi-faceted nature of the condition.

AUTHORS CONTRIBUTIONS

CJB and ACF conceived and drafted the article.

DECLARATION OF INTERESTS

CJB: none. ACF: none.

FIGURE LEGENDS

Figure 1. Conventional Subtyping of Rome IV IBS.

Figure 2. Novel Classification System for IBS Using Latent Class Analysis.

Figure 3. Novel Subgrouping of Rome IV IBS by Incorporating the Seven-Cluster Latent Class Model.

Figure 4. Novel Subgrouping of Rome IV IBS with Treatments Suggested According to Cluster.

REFERENCES

1. Ford AC, Sperber AD, Corsetti M, Camilleri M. Irritable bowel syndrome. Lancet. 2020;396:1675-88.

2. Oka P, Parr H, Barberio B, Black CJ, Savarino EV, Ford AC. Global prevalence of irritable bowel syndrome according to Rome III or IV criteria: A systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2020;5:908-17.

3. Goodoory VC, Ng CE, Black CJ, Ford AC. Direct healthcare costs of Rome IV or Rome III-defined irritable bowel syndrome in the United Kingdom. Aliment Pharmacol Ther. 2022;56:110-20.

4. Häuser W, Marschall U, Layer P, Grobe T. The prevalence, comorbidity, management and costs of irritable bowel syndrome. Dtsch Arztebl Int. 2019;116:463-70.

5. Zhang F, Xiang W, Li CY, Li SC. Economic burden of irritable bowel syndrome in China. World J Gastroenterol. 2016;22:10450-60.

6. Shin A, Xu H. Healthcare costs of irritable bowel syndrome and irritable bowel syndrome subtypes in the United States. Am J Gastroenterol. 2024;doi: 10.14309/ajg.0000000000002753.

7. Goodoory VC, Guthrie EA, Ng CE, Black CJ, Ford AC. Factors associated with lower disease-specific and generic health-related quality of life in Rome IV irritable bowel syndrome. Aliment Pharmacol Ther. 2023;57:323-34.

8. Drossman DA, Chang L, Schneck S, Blackman C, Norton WF, Norton NJ. A focus group assessment of patient perspectives on irritable bowel syndrome and illness severity. Dig Dis Sci. 2009;54:1532-41.

9. Farndale R, Roberts L. Long-term impact of irritable bowel syndrome: A qualitative study. Prim Health Care Res Dev. 2011;12:52-67.

10. Goodoory VC, Ng CE, Black CJ, Ford AC. Impact of Rome IV irritable bowel syndrome on work and activities of daily living. Aliment Pharmacol Ther. 2022;56:844-56.

11. Hearn M, Whorwell PJ, Vasant DH. Stigma and irritable bowel syndrome: A taboo subject? Lancet Gastroenterol Hepatol. 2020;5:607-15.

12. Goodoory VC, Ng CE, Black CJ, Ford AC. Willingness to accept risk with medication in return for cure of symptoms among patients with Rome IV irritable bowel syndrome. Aliment Pharmacol Ther. 2022;55:1311-9.

13. Drossman DA, Morris CB, Schneck S, Hu YJ, Norton NJ, Norton WF, et al. International survey of patients with IBS: Symptom features and their severity, health status, treatments, and risk taking to achieve clinical benefit. J Clin Gastroenterol. 2009;43:541-50.

14. Mearin F, Lacy BE, Chang L, Chey WD, Lembo AJ, Simren M, et al. Bowel disorders. Gastroenterology. 2016;150:1393-407.

15. Food and Drug Administration. Guidance for industry: Irritable bowel syndrome - clinical evaluation of drugs for treatment. https://www.fda.gov/media/78622/download. 2012. Accessed 1st June 2024.

16. European Medicines Agency. Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-medicinal-products-treatment-irritable-bowel-syndrome-revision-1_en.pdf. 2014. Accessed 1st June 2024.

17. Black CJ, Drossman DA, Talley NJ, Ruddy J, Ford AC. Functional gastrointestinal disorders: Advances in understanding and management. Lancet. 2020;396:1664-74.

18. Koloski NA, Jones M, Kalantar J, Weltman M, Zaguirre J, Talley NJ. The brain--gut pathway in functional gastrointestinal disorders is bidirectional: A 12-year prospective population-based study. Gut. 2012;61:1284-90.

19. Koloski NA, Jones M, Talley NJ. Evidence that independent gut-to-brain and brain-to-gut pathways operate in the irritable bowel syndrome and functional dyspepsia: A 1-year population-based prospective study. Aliment Pharmacol Ther. 2016;44:592-600.

20. Klem F, Wadhwa A, Prokop LJ, Sundt WJ, Farrugia G, Camilleri M, et al. Prevalence, risk factors, and outcomes of irritable bowel syndrome after infectious enteritis: A systematic review and meta-analysis. Gastroenterology. 2017;152:1042-54.e1.

21. Holtmann GJ, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. Lancet Gastroenterol Hepatol. 2016;1:133-46.

22. Drossman DA, Chang L, Chey WD, Kellow J, Tack J, Whitehead WE. The multidimensional clinical profile for functional gastrointestinal disorders: MDCP. 2nd ed ed. Raleigh, NC: Rome Foundation; 2016.

23. Polster A, Van Oudenhove L, Jones M, Ohman L, Tornblom H, Simren M. Mixture model analysis identifies irritable bowel syndrome subgroups characterised by specific profiles of gastrointestinal, extraintestinal somatic and psychological symptoms. Aliment Pharmacol Ther. 2017;46:529-39.

24. Polster AV, Palsson OS, Tornblom H, Ohman L, Sperber AD, Whitehead WE, et al. Subgroups of IBS patients are characterized by specific, reproducible profiles of GI and non-GI symptoms and report differences in healthcare utilization: A population-based study. Neurogastroenterol Motil. 2019;31:e13483.

25. Black CJ, Yiannakou Y, Guthrie EA, West R, Houghton LA, Ford AC. A novel method to classify and subgroup patients with IBS based on gastrointestinal symptoms and psychological profiles. Am J Gastroenterol. 2021;116:372-81.

26. Han CJ, Pike K, Jarrett ME, Heitkemper MM. Symptom-based latent classes of persons with irritable bowel syndrome. Res Nurs Health. 2019;42:382-91.

27. Byale A, Lennon RJ, Byale S, Breen-Lyles M, Edwinson AL, Gupta R, et al. High-dimensional clustering of 4000 irritable bowel syndrome patients reveals seven distinct disease subsets. Clin Gastroenterol Hepatol. 2024;22:173-84.

28. Black CJ, Yiannakou Y, Guthrie E, West R, Houghton LA, Ford AC. Longitudinal follow-up of a novel classification system for irritable bowel syndrome: Natural history and prognostic value. Aliment Pharmacol Ther. 2021;53:1126-37.

29. Black CJ, Ng CE, Goodoory VC, Ford AC. Novel symptom subgroups in individuals with irritable bowel syndrome predict disease impact and burden. Clin Gastroenterol Hepatol. 2024;22:386-96.

30. Sperber AD, Bangdiwala SI, Drossman DA, Ghoshal UC, Simren M, Tack J, et al. Worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome Foundation global study. Gastroenterology. 2021;160:99-114.

31. Black CJ, Houghton LA, West RM, Bangdiwala SI, Palsson OS, Sperber AD, et al. Novel irritable bowel syndrome subgroups are reproducible in the global adult population. Clin Gastroenterol Hepatol. 2024; doi: 10.1016/j.cgh.2024.05.042.

32. Lacy BE, Ford AC, Talley NJ. Quality of care and the irritable bowel syndrome: Is now the time to set standards? Am J Gastroenterol. 2018;113:167-9.

33. Owens DM, Nelson DK, Talley NJ. The irritable bowel syndrome: Long-term prognosis and the physician-patient interaction. Ann Intern Med. 1995;122:107-12.

34. Vasant DH, Paine PA, Black CJ, Houghton LA, Everitt HA, Corsetti M, et al. British Society of Gastroenterology guidelines on the management of irritable bowel syndrome. Gut. 2021;70:1214-40.

35. Drossman DA. 2012 David Sun lecture: Helping your patient by helping yourself--how to improve the patient-physician relationship by optimizing communication skills. Am J Gastroenterol. 2013;108:521-8.

36. Ringström G, Störsrud S, Posserud I, Lundqvist S, Westman B, Simrén M. Structured patient education is superior to written information in the management of patients with irritable bowel syndrome: A randomized controlled study. Eur J Gastroenterol Hepatol. 2010;22:420-8.

37. Saito YA, Prather CM, Van Dyke CT, Fett S, Zinsmeister AR, Locke Iii GR. Effects of multidisciplinary education on outcomes in patients with irritable bowel syndrome. Clin Gastroenterol Hepatol. 2004;2:576-84.

38. Labus J, Gupta A, Gill HK, Posserud I, Mayer M, Raeen H, et al. Randomised clinical trial: Symptoms of the irritable bowel syndrome are improved by a psycho-education group intervention. Aliment Pharmacol Ther. 2013;37:304-15.

39. Williams M, Barclay Y, Harper L, Marchant C, Seamark L, Hickson M. Feasibility, acceptability and cost efficiency of using webinars to deliver first-line patient education for people with Irritable Bowel Syndrome as part of a dietetic-led gastroenterology service in primary care. J Hum Nutr Diet. 2020;33:758-66.

40. Schuch FB, Vancampfort D, Firth J, Rosenbaum S, Ward PB, Silva ES, et al. Physical activity and incident depression: A meta-analysis of prospective cohort studies. Am J Psychiatry. 2018;175:631-48.

41. McDowell CP, Dishman RK, Gordon BR, Herring MP. Physical activity and anxiety: A systematic review and meta-analysis of prospective cohort studies. Am J Prev Med. 2019;57:545-56.

42. Warburton DER, Bredin SSD. Health benefits of physical activity: A systematic review of current systematic reviews. Curr Opin Cardiol. 2017;32:541-56.

43. Villoria A, Serra J, Azpiroz F, Malagelada JR. Physical activity and intestinal gas clearance in patients with bloating. Am J Gastroenterol. 2006;101:2552-7.

44. Strid H, Simrén M, Störsrud S, Stotzer PO, Sadik R. Effect of heavy exercise on gastrointestinal transit in endurance athletes. Scand J Gastroenterol. 2011;46:673-7.

45. Daley AJ, Grimmett C, Roberts L, Wilson S, Fatek M, Roalfe A, et al. The effects of exercise upon symptoms and quality of life in patients diagnosed with irritable bowel syndrome: A randomised controlled trial. Int J Sports Med. 2008;29:778-82.

46. Johannesson E, Simren M, Strid H, Bajor A, Sadik R. Physical activity improves symptoms in irritable bowel syndrome: A randomized controlled trial. Am J Gastroenterol. 2011;106:915-22.

47. Johannesson E, Ringstrom G, Abrahamsson H, Sadik R. Intervention to increase physical activity in irritable bowel syndrome shows long-term positive effects. World J Gastroenterol. 2015;21:600-8.

48. Nunan D, Cai T, Gardener AD, Ordóñez-Mena JM, Roberts NW, Thomas ET, et al. Physical activity for treatment of irritable bowel syndrome. Cochrane Database Syst Rev. 2022;6:CD011497.

49. Blanchard EB, Lackner JM, Jaccard J, Rowell D, Carosella AM, Powell C, et al. The role of stress in symptom exacerbation among IBS patients. J Psychosom Res. 2008;64:119-28.

50. Dancey CP, Taghavi M, Fox RJ. The relationship between daily stress and symptoms of irritable bowel: A time-series approach. J Psychosom Res. 1998;44:537-45.

51. Chang L. The role of stress on physiologic responses and clinical symptoms in irritable bowel syndrome. Gastroenterology. 2011;140:761-5.

52. Vanuytsel T, van Wanrooy S, Vanheel H, Vanormelingen C, Verschueren S, Houben E, et al. Psychological stress and corticotropin-releasing hormone increase intestinal permeability in humans by a mast cell-dependent mechanism. Gut. 2014;63:1293-9.

53. Horn A, Stangl S, Parisi S, Bauer N, Roll J, Löffler C, et al. Systematic review with meta-analysis: Stress-management interventions for patients with irritable bowel syndrome. Stress Health. 2023;39:694-707.

54. Hookway C, Buckner S, Crosland P, Longson D. Irritable bowel syndrome in adults in primary care: Summary of updated NICE guidance. BMJ. 2015;350:h701.

55. Ballou S, Alhassan E, Hon E, Lembo C, Rangan V, Singh P, et al. Sleep disturbances are commonly reported among patients presenting to a gastroenterology clinic. Dig Dis Sci. 2018;63:2983-91.

56. Vege SS, Locke Iii GR, Weaver AL, Farmer SA, Melton Iii LJ, Talley NJ. Functional gastrointestinal disorders among people with sleep disturbances: A population-based study. Mayo Clin Proc. 2004;79:1501-6.

57. Topan R, Vork L, Fitzke H, Pandya S, Keszthelyi D, Cornelis J, et al. Poor subjective sleep quality predicts symptoms in irritable bowel syndrome Using the experience sampling method. Am J Gastroenterol. 2024;119:155-64.

58. Koloski NA, Jones M, Walker MM, Keely S, Holtmann G, Talley NJ. Sleep disturbances in the irritable bowel syndrome and functional dyspepsia are independent of psychological distress: A population-based study of 1322 Australians. Aliment Pharmacol Ther. 2021;54:627-36.

59. de Vries J, Miller PE, Verbeke K. Effects of cereal fiber on bowel function: A systematic review of intervention trials. World J Gastroenterol. 2015;21:8952-63.

60. Müller M, Canfora EE, Blaak EE. Gastrointestinal transit time, Glucose homeostasis and metabolic health: modulation by dietary fibers. Nutrients. 2018;10:275.

61. Algera J, Colomier E, Simrén M. The dietary management of patients with irritable bowel syndrome: A narrative review of the existing and emerging evidence. Nutrients. 2019;11:2162.

62. Moayyedi P, Quigley EM, Lacy BE, Lembo AJ, Saito YA, Schiller LR, et al. The effect of fiber supplementation on irritable bowel syndrome: A systematic review and meta-analysis. Am J Gastroenterol. 2014;109:1367-74.

63. Francis CY, Whorwell PJ. Bran and irritable bowel syndrome: time for reappraisal. Lancet. 1994;344:39-40.

64. Suares NC, Ford AC. Systematic review: The effects of fibre in the management of chronic idiopathic constipation. Aliment Pharmacol Ther. 2011;33:895-901.

65. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014;11:506-14.

66. Goodoory VC, Khasawneh M, Black CJ, Quigley EMM, Moayyedi P, Ford AC. Efficacy of probiotics in irritable bowel syndrome: Systematic review and meta-analysis. Gastroenterology. 2023;165:1206-18.

67. British Dietetic Association. Irritable bowel syndrome and diet, https://www.bda.uk.com/resource/irritable-bowel-syndrome-diet.html. Accessed 1st June 2024.

68. Black CJ, Staudacher HM, Ford AC. Efficacy of a low FODMAP diet in irritable bowel syndrome: systematic review and network meta-analysis. Gut. 2022;71:1117-26.

69. Carbone F, Van den Houte K, Besard L, Tack C, Arts J, Caenepeel P, et al. Diet or medication in primary care patients with IBS: the DOMINO study - a randomised trial supported by the Belgian Health Care Knowledge Centre (KCE Trials Programme) and the Rome Foundation Research Institute. Gut. 2022;71:2226-32.

70. Chapman RW, Stanghellini V, Geraint M, Halphen M. Randomized clinical trial: Macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. Am J Gastroenterol. 2013;108:1508-15.

71. Awad RA, Camacho S. A randomized, double-blind, placebo-controlled trial of polyethylene glycol effects on fasting and postprandial rectal sensitivity and symptoms in hypersensitive constipation-predominant irritable bowel syndrome. Colorectal Dis. 2010;12:1131-8.

72. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idipathic constipation: Systematic review and meta-analysis. Gut. 2011;60:209-18.

73. Black CJ, Ford AC. Irritable bowel syndrome: A spotlight on future research needs. Lancet Gastroenterol Hepatol. 2021;6:419-22.

74. Ford AC, Brandt LJ, Young C, Chey WD, Foxx-Orenstein AE, Moayyedi P. Efficacy of 5-HT 3 antagonists and 5-HT 4 agonists in irritable bowel syndrome: Systematic review and meta-analysis. Am J Gastroenterol. 2009;104:1831-43.

75. Tack J, Camilleri M, Chang L, Chey WD, Galligan JJ, Lacy BE, et al. Systematic review: Cardiovascular safety profile of 5-HT(4) agonists developed for gastrointestinal disorders. Aliment Pharmacol Ther. 2012;35:745-67.

76. Rao S, Lembo AJ, Shiff SJ, Lavins BJ, Currie MG, Jia XD, et al. 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. Am J Gastroenterol. 2012;107:1714-24.

77. Brenner DM, Fogel R, Dorn SD, Krause R, Eng P, Kirshoff R, et al. Efficacy, safety, and tolerability of plecanatide in patients with irritable bowel syndrome with constipation: Results of two phase 3 randomized clinical trials Am J Gastroenterol. 2018;113:735-45.

78. Chey WD, Lembo AJ, Rosenbaum DP. Efficacy of tenapanor in treating patients with irritable bowel syndrome with constipation: A 12-week, placebo-controlled phase 3 trial (T3MPO-1). Am J Gastroenterol. 2020;115:281-93.

79. Black CJ, Burr NE, Quigley EMM, Moayyedi P, Houghton LA, Ford AC. Efficacy of secretagogues in patients with irritable bowel syndrome with constipation: Systematic review and network meta-analysis. Gastroenterology. 2018;155:1753-63.

80. Nelson AD, Black CJ, Houghton LA, Lacy MQ, Ford AC. Systematic review and network meta-analysis: Efficacy of licensed drugs for abdominal bloating in irritable bowel syndrome with constipation. Aliment Pharmacol Ther. 2021;54:98-108.

81. Lavo B, Stenstam M, Nielsen AL. Loperamide in treatment of irritable bowel syndrome - A double-blind placebo controlled study. Scand J Gastroenterol. 1987;130:77-80.

82. Hovdenak N. Loperamide treatment of the irritable bowel syndrome. Scand J Gastroenterol. 1987;130:81-4.

83. Ford AC, Moayyedi P, Chey WD, Harris LA, Lacy BE, Saito YA, et al. American College of Gastroenterology monograph on management of irritable bowel syndrome. Am J Gastroenterol. 2018;113 (Suppl 2):1-18.

84. Lacy BE, Chey WD, Cash BD, Lembo AJ, Dove LS, Covington PS. Eluxadoline efficacy in IBS-D patients who report prior loperamide use. Am J Gastroenterol. 2017;112:924-32.

85. Howell CA, Markaryan E, Allgar V, Kemppinen A, Khovanov A, Pandya P, et al. Enterosgel for the treatment of adults with acute diarrhoea in a primary care setting: A randomised controlled trial. BMJ Open Gastroenterol. 2019;6:e000287.

86. Howell CA, Kemppinen A, Allgar V, Dodd M, Knowles CH, McLaughlin J, et al. Double-blinded randomised placebo controlled trial of enterosgel (polymethylsiloxane polyhydrate) for the treatment of IBS with diarrhoea (IBS-D). Gut. 2022;71:2430-8.

87. Eswaran SL, Chey WD, Han-Markey T, Ball S, Jackson K. A randomized controlled trial comparing the low FODMAP diet vs. modified NICE guidelines in US adults with IBS-D. Am J Gastroenterol. 2016;111:1824-32.

88. Gorard DA, Libby GW, Farthing MJ. Influence of antidepressants on whole gut orocaecal transit times in health and irritable bowel syndrome. Aliment Pharmacol Ther. 1994;8:159-66.

89. Gorard DA, Libby GW, Farthing MJ. Effect of a tricyclic antidepressant on small intestinal motility in health and diarrhea-predominant irritable bowel syndrome. Dig Dis Sci. 1995;40:86-95.

90. Drossman DA, Tack J, Ford AC, Szigethy E, Tornblom H, Van Oudenhove L. Neuromodulators for functional gastrointestinal disorders (disorders of gut-brain interaction): A Rome Foundation working team report. Gastroenterology. 2018;154:1140-71.e1.

91. Vahedi H, Merat S, Momtahen S, Kazzazi AS, Ghaffari N, Olfati G, et al. Clinical trial: The effect of amitriptyline in patients with diarrhea-predominant irritable bowel syndrome. Aliment Pharmacol Ther. 2008;27:678-84.

92. Fodor AA, Pimentel M, Chey WD, Lembo A, Golden PL, Israel RJ, et al. Rifaximin is associated with modest, transient decreases in multiple taxa in the gut microbiota of patients with diarrhoea-predominant irritable bowel syndrome. Gut Microbes. 2019;10:22-33.

93. Zeber-Lubecka N, Kulecka M, Ambrozkiewicz F, Paziewska A, Goryca K, Karczmarski J, et al. Limited prolonged effects of rifaximin treatment on irritable bowel syndrome-related differences in the fecal microbiome and metabolome. Gut Microbes. 2016;7:397-413.

94. Chey WD, Shah ED, DuPont HL. Mechanism of action and therapeutic benefit of rifaximin in patients with irritable bowel syndrome: A narrative review. Therap Adv Gastroenterol. 2020;13:1756284819897531.

95. Ford AC, Spiegel BMR, Talley NJ, Moayyedi P. Small intestinal bacterial overgrowth in irritable bowel syndrome: Systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2009;7:1279-86.

96. Fukudo S, Kinoshita Y, Okumura T, Ida M, Akiho H, Nakashima Y, et al. Ramosetron reduces symptoms of irritable bowel syndrome with diarrhea and improves quality of life in women. Gastroenterology. 2016;150:358-66.

97. Lembo AJ, Lacy BE, Zuckerman MJ, Schey R, Dove LS, Andrae DA, et al. Eluxadoline for irritable bowel syndrome with diarrhea. N Engl J Med. 2016;374:242-53.

98. Pimentel M, Lembo A, Chey WD, Zakko S, Ringel Y, Yu J, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med. 2011;364:22-32.

99. Black CJ, Burr NE, Camilleri M, Earnest DL, Quigley EM, Moayyedi P, et al. Efficacy of pharmacological therapies in patients with IBS with diarrhoea or mixed stool pattern: Systematic review and network meta-analysis. Gut. 2020;69:74-82.

100. Lembo AJ, Olden KW, Ameen VZ, Gordon SL, Heath AT, Carter EG. Effect of alosetron on bowel urgency and global symptoms in women with severe, diarrhea-

predominant irritable bowel syndrome: Analysis of two controlled trials. Clin Gastroenterol Hepatol. 2004;2:675-82.

101. Fukudo S, Ida M, Akiho H, Nakashima Y, Matsueda K. Effect of ramosetron on stool consistency in male patients with irritable bowel syndrome with diarrhea. Clin Gastroenterol Hepatol. 2014;12:953-9.e4.

102. Harinstein L, Wu E, Brinker A. Postmarketing cases of eluxadoline-associated pancreatitis in patients with or without a gallbladder. Aliment Pharmacol Ther. 2018;47:809-15.

103. Chang L, Chey WD, Harris L, Olden K, Surawicz C, Schoenfeld P. Incidence of ischemic colitis and serious complications of constipation among patients using alosetron: Systematic review of clinical trials and post-surveillance marketing data. Am J Gastroenterol. 2006;101:1069-79.

104. Lacy BE, Nicandro JP, Chuang E, Earnest DL. Alosetron use in clinical practice: significant improvement in irritable bowel syndrome symptoms evaluated using the US Food and Drug Administration composite endpoint. Therap Adv Gastroenterol. 2018;11:1756284818771674.

105. Gunn D, Topan R, Barnard L, Fried R, Holloway I, Brindle R, et al. Randomised, placebo-controlled trial and meta-analysis show benefit of ondansetron for irritable bowel syndrome with diarrhoea: The TRITON trial. Aliment Pharmacol Ther. 2023;57:1258-71.

106. Hawthorn M, Ferrante J, Luchowski E, Rutledge A, Wei XY, Triggle DJ. The actions of peppermint oil and menthol on calcium channel dependent processes in intestinal, neuronal and cardiac preparations. Aliment Pharmacol Ther. 1988;2:101-18.

107. Karashima Y, Damann N, Prenen J, Talavera K, Segal A, Voets T, et al. Bimodal action of menthol on the transient receptor potential channel TRPA1. J Neurosci. 2007;27:9874-84.

108. Black CJ, Yuan Y, Selinger CP, Camilleri M, Quigley EMM, Moayyedi P, et al. Efficacy of soluble fibre, antispasmodic drugs, and gut-brain neuromodulators in irritable bowel syndrome: A systematic review and network meta-analysis. Lancet Gastroenterol Hepatol. 2020;5:117-31.

109. Ingrosso MR, Ianiro G, Nee J, Lembo AJ, Moayyedi P, Black CJ, et al. Systematic review and meta-analysis: Efficacy of peppermint oil in irritable bowel syndrome. Aliment Pharmacol Ther. 2022;56:932-41.

110. Nee J, Ballou S, Kelley JM, Kaptchuk TJ, Hirsch W, Katon J, et al. Peppermint oil treatment for irritable bowel syndrome: A randomized placebo-controlled trial. Am J Gastroenterol. 2021;116:2279-85.

111. Weerts ZZRM, Masclee AAM, Witteman BJM, Clemens CHM, Winkens B, Brouwers JRBJ, et al. Efficacy and safety of peppermint oil in a randomized double-blind trial of patients with irritable bowel syndrome. Gastroenterology. 2020;158:123-36.

112. Thoua NM, Murray CD, Winchester WJ, Roy AJ, Pitcher MC, Kamm MA, et al. Amitriptyline modifies the visceral hypersensitivity response to acute stress in the irritable bowel syndrome. Aliment Pharmacol Ther. 2009;29:552-60.

113. Ford AC, Lacy BE, Harris LA, Quigley EM, Moayyedi P. Effect of antidepressants and psychological therapies in irritable bowel syndrome: An updated systematic review and meta-analysis. Am J Gastroenterol. 2019;114:21-39.

114. Ford AC, Wright-Hughes A, Alderson SL, Ow PL, Ridd MJ, Foy R, et al. Amitriptyline at low-dose and titrated for irritable bowel syndrome as second-line treatment in primary care (ATLANTIS): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2023;402:1773-85.

115. Kuiken SD, Tytgat GNJ, Boeckxstaens GEE. The selective serotonin reuptake inhibitor fluoxetine does not change rectal sensitivity and symptoms in patients with irritable bowel syndrome: A double-blind, randomized, placebo-controlled study. Clin Gastroenterol Hepatol. 2003;1:219-28.

116. Vahedi H, Merat S, Rashidioon A, Ghoddoosi A, Malekzadeh R. The effect of fluoxetine in patients with pain and constipation-predominant irritable bowel syndrome: A double-blind randomized-controlled study. Aliment Pharmacol Ther. 2005;22:381-5.

117. Sharbafchi MR, Afshar H, Adhamian P, Feizi A, Daghaghzadeh H, Adibi P. Effects of venlafaxine on gastrointestinal symptoms, depression, anxiety, stress, and quality of life in patients with the moderate-to-severe irritable bowel syndrome. J Res Med Sci. 2020; 25:115.

118. Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, Shaw JL, Thompson L, Nelson DL, et al. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. Neuropsychopharmacology. 2001;25:871-80.

119. Sikka P, Kaushik S, Kumar G, Kapoor S, Bindra VK, Saxena KK. Study of antinociceptive activity of SSRI (fluoxetine and escitalopram) and atypical antidepressants (venlafaxine and mirtazepine) and their interaction with morphine and naloxone in mice. J Pharm Bioallied Sci. 2011;3:412-6.

120. Sharbafchi MR, Afshar Zanjani H, Saneian Z, Feizi A, Daghaghzadeh H, Adibi P. Effects of duloxetine on gastrointestinal symptoms, depression, anxiety, stress, and quality of life in patients with the moderate-to-severe irritable bowel syndrome. Adv Biomed Res. 2023;12:249.

121. Salehian R, Mokhtare M, Ghanbari Jolfaei A, Noorian R. Investigation the effectiveness of duloxetine in quality of life and symptoms of patients with irritable bowel syndrome. Adv Biomed Res. 2021;10:14.

122. Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. Cochrane Database Syst Rev. 2014(1):CD007115.

123. Skljarevski V, Ossanna M, Liu-Seifert H, Zhang Q, Chappell A, Iyengar S, et al. A double-blind, randomized trial of duloxetine versus placebo in the management of chronic low back pain. Eur J Neurol. 2009;16:1041-8.

124. Skljarevski V, Zhang S, Desaiah D, Alaka KJ, Palacios S, Miazgowski T, et al. Duloxetine versus placebo in patients with chronic low back pain: A 12-week, fixed-dose, randomized, double-blind trial. J Pain. 2010;11:1282-90.

125. Chang L, Lembo A, Sultan S. Spotlight: IBS treatment. Gastroenterology. 2022;163:153.

126. Goodoory VC, Khasawneh M, Thakur ER, Everitt HA, Gudleski GD, Lackner JM, et al. Effect of brain-gut behavioral treatments on abdominal pain in irritable bowel syndrome: Systematic review and network meta-analysis. Gastroenterology. 2024;doi: 10.1053/j.gastro.2024.05.010.

127. Kilgallon E, Vasant DH, Green D, Shields PL, Hamdy S, Lal S, et al. Chronic continuous abdominal pain: Evaluation of diagnostic features, iatrogenesis and drug treatments in a cohort of 103 patients. Aliment Pharmacol Ther. 2019;49:1282-92.

128. Staudacher HM, Black CJ, Teasdale SB, Mikocka-Walus A, Keefer L. Irritable bowel syndrome and mental health comorbidity - approach to multidisciplinary management. Nat Rev Gastroenterol Hepatol. 2023;20:582-96.

129. Drossman DA, Toner BB, Whitehead WE, Diamant NE, Dalton CB, Duncan S, et al. Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders. Gastroenterology. 2003;125:19-31.

130. National Institute for Health and Care Excellence. Depression in adults with a chronic physical health problem: recognition and management. https://www.nice.org.uk/guidance/cg91. 2009. Accessed 1st June 2024.

131. Tack J, Broekaert D, Fischler B, van Oudenhove L, Gevers AM, Janssens J. A controlled crossover study of the selective serotonin reuptake inhibitor citalopram in irritable bowel syndrome. Gut. 2006;55:1095-103.

132. Lewis-Fernández R, Lam P, Lucak S, Galfalvy H, Jackson E, Fried J, et al. An open-label pilot study of duloxetine in patients with irritable bowel syndrome and comorbid major depressive disorder. J Clin Psychopharmacol. 2016;36:710-5.

133. Everitt HA, Landau S, O'Reilly G, Sibelli A, Hughes S, Windgassen S, et al. Assessing telephone-delivered cognitive-behavioural therapy (CBT) and web-delivered CBT versus treatment as usual in irritable bowel syndrome (ACTIB): A multicentre randomised trial. Gut. 2019;68:1613-23.

134. Everitt HA, Landau S, O'Reilly G, Sibelli A, Hughes S, Windgassen S, et al. Cognitive behavioural therapy for irritable bowel syndrome: 24-month follow-up of participants in the ACTIB randomised trial. Lancet Gastroenterol Hepatol. 2019;4:863-72.

135. Lindfors P, Unge P, Arvidsson P, Nyhlin H, Bjornsson E, Abrahamsson H, et al. Effects of gut-directed hypnotherapy on IBS in different clinical settings - Results from two randomized, controlled trials. Am J Gastroenterol. 2012;107:276-85.

136. Moser G, Tragner S, Elwira Gajowniczek E, Mikulits A, Michalski M, Kazemi-Shirazi L, et al. Long-term success of GUT-directed group hypnosis for patients with refractory irritable bowel syndrome: A randomized controlled trial. Am J Gastroenterol. 2013;108:602-9.

137. Pampallona S, Bollini P, Tibaldi G, Kupelnick B, Munizza C. Combined pharmacotherapy and psychological treatment for depression: A systematic review. Arch Gen Psychiatry. 2004;61:714-9.

138. Holroyd KA, O'Donnell FJ, Stensland M, Lipchik GL, Cordingley GE, Carlson BW. Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: A randomized controlled trial. JAMA. 2001;285:2208-15.

139. Lackner JM, Jaccard J, Krasner SS, Katz LA, Gudleski GD, Blanchard EB. How does cognitive behavior therapy for irritable bowel syndrome work? A mediational analysis of a randomized clinical trial. Gastroenterology. 2007;133:433-44.

140. Keefer L, Palsson OS, Pandolfino JE. Best practice update: Incorporating psychogastroenterology into management of digestive disorders. Gastroenterology. 2018;154:1249-57.

141. Basnayake C, Kamm MA, Stanley A, Wilson-O'Brien A, Burrell K, Lees-Trinca I, et al. Standard gastroenterologist versus multidisciplinary treatment for functional gastrointestinal disorders (MANTRA): An open-label, single-centre, randomised controlled trial. Lancet Gastroenterol Hepatol. 2020;5:890-9.