Non-pharmaceutical treatments for irritable bowel syndrome

Xiao Jing Wang,[1] Elyse Thakur,[2,3] Jordan Shapiro[4]

[1]Mayo Clinic Rochester, MN, USA
[2]Atrium Health, Charlotte, NC, USA
[3]Wake Forest University School of Medicine, Winston-Salem, NC, USA
[4]Gentle GI, Houston, TX, USA
Correspondence to: X J Wang
Wang.xiao@mayo.edu

Cite this as: *BMJ* 2024;387:e075777
http://dx.doi.org/10.1136/bmj-2023-075777

Series explanation: State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason they are written predominantly by US authors.

ABSTRACT

Irritable bowel syndrome (IBS) is a chronic disorder of gut-brain interaction that impacts a significant portion of the population and is associated with substantial morbidity, reduced quality of life, and economic impact globally. The pathophysiology of IBS is complex and incompletely understood, and the heterogeneity of IBS is reflected in the variety of pharmaceutical and non-pharmaceutical therapies utilized for the management of IBS. Given limitations with pharmaceutical treatments, many patients with IBS seek non-pharmaceutical options. Several non-pharmaceutical treatments such as the low FODMAP diet and brain-gut behavior interventions such as gut directed hypnosis and cognitive behavioral therapy are now considered standard of care and are part of all major guidelines for the treatment of IBS. However, challenges with access to and optimal implementation of these therapies remain. This review focuses on the current evidence for common non-pharmaceutical treatments for IBS, including the latest advances in dietary and brain-gut behavioral care, in addition other complementary and integrative health practices and emerging therapies.

Introduction

Irritable bowel syndrome (IBS) is a chronic disorder of gut-brain interaction characterized by abdominal pain and change in the consistency and/or frequency of stools. Pathophysiology mechanisms are thought to be multifactorial involving altered brain-gut axis, increased visceral hypersensitivity, and gut microbial dysbiosis, among others that interact to produce symptoms (fig 1). Symptoms range from mild and intermittent to severe and daily.

Despite several treatment options and consensus guidelines for the treatment of IBS, patients and providers are challenged by high costs of pharmaceutical treatments and tolerability.[1] Patient interest in non-pharmaceutical treatment is multifactorial, including preferences for more natural treatments and/or perception of greater safety.[2 3] US based guidelines by the American Gastroenterological Association (AGA) for the pharmacological treatment of irritable bowel syndrome with diarrhea (IBS-D) and irritable bowel syndrome with constipation (IBS-C), which are not within the scope of this article, are available for guidance on available pharmaceutical treatment options.[4 5] This review aims to highlight current and emerging non-pharmaceutical treatment options for IBS to aid general practitioners and gastroenterologists in expanding their clinical toolkit for this common disorder. Emerging treatments include novel treatment approaches that are promising but in need of further study. Emerging treatments that are derived from established approaches are discussed within the section; those that are novel are presented separately. International guideline consensus for non-pharmaceutical options, when included, is summarized in table 1.

Epidemiology

IBS has a global prevalence of about 4% in adults with female predominance (5.2% in females *v* 2.9% in males) and declining prevalence with age (5.3% in 18-39 years old *v* 1.7% in those >65 years old).[14] The Second Asian Consensus and Indian Society of Gastroenterology IBS guidelines report equal sex prevalence.[11 12] IBS does not increase mortality, but patients experience substantial morbidity with impaired quality of life.[15] In a survey of 1885 patients with IBS, symptoms affected productivity 8.0 days with 1.5 days of missed school or work per month. In exchange for one month of relief from IBS, more than half of patients surveyed would give up caffeine or alcohol, 40% would give up sex, 24.5% would give up cell phones, and 21.5% would give up the internet for one month.[16] Another study found that IBS patients would sacrifice 10-15 years of life expectancy for an immediate cure.[17]

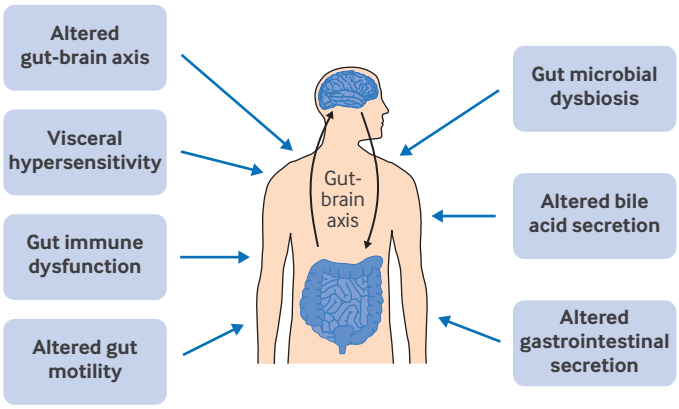

Fig 1 | Pathophysiology of irritable bowel syndrome (IBS) is thought to be multifactorial, involving an interaction among factors including genetic predisposition, altered brain-gut axis, increased visceral hypersensitivity, increased mucosal permeability, bile acid malabsorption, gut microbial dysbiosis, altered mucosal immune function, and altered motility. The interplay of these alterations culminates in patient symptoms. Adapted from figures from Mayo Clinic Media Library and Dreamstime.com (image ID 113236410 ©Kateryna Kon)

A study of direct (eg, healthcare professional consultations) and indirect (eg, absenteeism, presenteeism, and productivity loss due to unpaid labor) costs found quarterly mean total costs per patient of $2444 (£1907; €2262), with indirect costs ($1525) greater than direct ones ($909). Mental healthcare visits made up a greater portion of direct care costs than gastroenterology visits.[18] Health economics studies suggest that from a payor and utilization standpoint, targeting global symptoms with non-pharmaceutical options such as diet and cognitive behavioral therapy (CBT), as well as neuromodulators is more cost effective with similar health outcomes, largely because of prescription drug costs.[19] From a patient perspective, insurance covered drug options are more cost effective owing to lack of reimbursement and out of pocket costs for many non-pharmaceutical options.[20] Short and long term costs, including accounting for treatment durability, need to be considered when choosing a treatment plan.

Sources and selection criteria

We searched the literature utilizing PubMed from March 2013 to March 2023 searching "Irritable Bowel Syndrome" or "IBS" and "treatment" filtered by clinical trial, meta-analysis, randomized controlled trial, and systematic reviews in adult, human subjects. This initial search yielded 992 articles. A second search was undertaken of APA PsycINFO, EBM Reviews-Cochrane Central Register of controlled trials and systematic reviews, Embase, and Ovid MedLine from inception to 2023. These were cross referenced and added to the initial search for comprehensive review. This yielded a total of 1582 articles that were manually reviewed by at least two authors per article for relevance and rigor of the research conducted. The heterogeneous nature of non-pharmaceutical treatments and vast breadth of therapeutics that have been tried in the treatment of IBS meant that interventions included were selected on the basis of inclusion in currently available guidelines, availability of robust evidence, approval of the US Food and Drug Administration, and in consultation with patient advocates. Studies were included if they were primary randomized clinical trials (RCTs) or systematic reviews or meta-analyses. Randomized trials that were small in size were included and mentioned as such if study methodology was of high quality; low quality individual RCTs were not included. Pharmaceutical treatments, basic science studies, pediatric studies, case studies, and pathophysiology (non-treatment) studies were excluded. Narrative review articles were included to review references to primary trials, which were then included if relevant. In the case of highly relevant articles published after the search period, all three authors were required to agree on addition to the manuscript.

Diet

Dietary management of IBS is important to patients and providers. Fiber, in dietary and supplement form, is a mainstay of treatment for IBS and is recommended in multiple guidelines as front line therapy for global symptom improvement as defined by the FDA as a primary outcome of IBS therapeutics (includes overall wellbeing and symptom severity).[7] A survey found that more than 80% of IBS patients reported food related symptoms, with greater numbers of culprit foods reported in patients with more severe IBS.[21] Therefore, restrictive or elimination diets are often tried. These diets range from specific food restrictions (eg, lactose free or gluten free diets), to larger dietary shifts such as the Mediterranean diet, the National Institute for Health and Care Excellence (NICE) dietary guidance, or a low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet. In a survey of >1500 gastroenterologists, roughly 60% reported that patients link food with symptoms, and most utilized a trial and error approach or lactose/gluten-free diets. Fewer used the low FODMAP diet,[22] often because of the lack of registered dietitian with suitable expertise. Although many variations of elimination and restrictive diets exist, this review is limited to diets recommended by guidelines and those with evidence in IBS treatment (table 2).

Fiber

Dietary fibers are a variety of non-digestible plant based carbohydrates that are not absorbed by the small intestine and differentially impact the digestive system depending on interaction with colonic microbiota,[24] Insoluble fibers are found in peelings of fruits and vegetables, seed, whole grains, and wheat bran; they increase stool bulk while stimulating colonic motility and mucus production. This can contribute to common IBS symptoms such as bloating and abdominal discomfort.[7] Soluble fiber is found in psyllium (synonymous with ispaghula husk), corn fiber, calcium polycarbophil,

Table 1 | Summary of non-pharmaceutical interventions for IBS in international guidelines

	Fiber	Diet	Probiotics	Complementary and integrative health*	Brain gut behavioral therapies	Mind/body movement	Fecal microbiota transplant
British Society of Gastroenterology 2021[6]	Soluble fiber recommended for global IBS symptoms; avoid insoluble fiber Recommend 3-4 g/day initially and increase gradually *Strong recommendation; moderate quality of evidence*	Initial dietary advice should be offered to all patients Strong recommendation; weak quality of evidence Low FODMAP diet recommended as second line dietary treatment for global IBS symptoms and abdominal pain under guidance of a dietitian Weak recommendation; very low quality evidence Gluten-free diet not recommended Weak recommendation; very low quality evidence	May be effective for global IBS symptoms and abdominal pain, but no specific strain or species recommended Recommend trial for up to 12 weeks Weak recommendation; very low quality evidence	Peppermint oil might be effective as initial treatment for global IBS symptoms and abdominal pain Weak recommendation; very low quality evidence	Gut directed CBT and gut directed hypnotherapy may be efficacious for global IBS symptoms Strong recommendation; low quality evidence Consider psychological therapies when symptoms have not improved after 12 months of drug treatment Strong recommendation; low quality evidence	Regular exercise recommended as initial treatment Strong recommendation; weak quality of evidence	
American Gastroenterological Association 2020-2022[7 8]	Soluble fiber for global IBS symptoms Goal is about 25-35 g/day intake from supplements and food (best practice advice)	Low FODMAP diet is the most evidence based NICE dietary guidance has benefit Screen for disordered eating RCTs show mixed results for gluten-free diet (best practice advice)	Only recommended in the context of clinical trials		Should be considered on an individual basis		
American College of Gastroenterology 2021[9]	Suggest soluble, but not insoluble, fiber to treat global IBS symptoms *Strong recommendation; moderate quality of evidence*	Recommend limited trial of low FODMAP diet to improve global IBS symptoms Conditional recommendation; very low quality evidence	Suggest against use for global IBS symptoms Conditional recommendation; very low quality evidence	Peppermint oil suggested for global IBS symptoms Conditional recommendation; low quality evidence	Suggest gut directed psychotherapies for global IBS symptoms Conditional recommendation; very low quality evidence		Recommend against use for global IBS symptoms Strong recommendation; very low quality evidence
Joint Consensus of Italian Societies 2023[10]	Recommend soluble but not insoluble, fiber for global IBS symptoms Strong recommendation; low quality evidence	Recommend traditional dietary advice as initial treatment Strong recommendation; very low quality evidence Low FODMAP as second line treatment Conditional recommendation; low quality evidence Gluten-free diet not recommended Strong recommendation; very low quality evidence	Recommend probiotics as a group for global IBS symptoms or abdominal pain Conditional recommendation; low quality evidence	Recommend against use of cannabinoid and endocannabinoid modulators Conditional recommendation; low quality evidence Recommend against use of complementary and alternative therapies (although some reasonably good quality evidence exists for specific approaches) Conditional recommendation; low quality evidence	Recommend psychologically directed therapies for global IBS symptoms Strong recommendation; low quality evidence		Recommend against use Strong recommendation; low quality evidence
Indian Neurogastroenterology and Motility Association 2023[11]	Soluble fiber suggested as a laxative but lacks high quality evaluation of efficacy	Dietary restriction of FODMAP is useful in a proportion of patients Grade A recommendation Level of evidence: I	Probiotics may be helpful, but more studies are needed Grade B recommendation Level of evidence: II-2		Psychological interventions are useful in those with psychological comorbidity or refractory IBS Grade B recommendation Level of evidence: II-1		
Second Asian Consensus 2019[12]		Low FODMAP diet could be helpful Moderate grade evidence	Effectiveness not fully validated Moderate grade evidence	Some complementary and alternative medicine, specifically peppermint oil and Japanese Kampo medicine could be considered effective in treating IBS symptoms Low grade evidence Traditional Chinese medicines including herbal and patent prescriptions could be helpful for some; high quality RCTs are needed to evaluate efficacy Moderate grade evidence	Psychotherapy is possibly useful in tertiary care patients Low grade evidence		
Canadian Association of Gastroenterology 2019[13]	Recommend psyllium supplementation for IBS symptoms *Strong recommendation; moderate quality evidence* Suggest against wheat bran supplementation Conditional recommendation; low quality evidence	Low FODMAP diet suggested to reduce IBS symptoms Suggest against gluten-free diet Conditional Recommendation; very low quality evidence	Suggest probiotics for global IBS symptoms Conditional recommendation; low quality evidence	Suggest against herbal remedies Conditional recommendation; very low quality evidence Recommend against offering acupuncture for global IBS symptoms Strong recommendation; very low quality evidence Suggest peppermint oil for global IBS symptoms Conditional recommendation; low quality evidence	Suggest CBT and suggest hypnotherapy for global IBS symptoms Both conditional recommendations; very low quality evidence		

*Includes peppermint oil and cannabis.
CBT=cognitive behavioral therapy; FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS=irritable bowel syndrome; NICE=National Institute for Health and Clinical Excellence; RCT=randomized controlled trial.

Table 2 | Diet guidelines

	Single food elimination diet*	Mediterranean diet	NICE diet	Low FODMAP diet
Principle	Elimination of specific non-tolerated food from diet	Diet based on traditional foods consumed in Mediterranean countries shown to have multiple health benefits[23]	Holistic approach to reduce potential symptom triggers or exacerbating factors and to modify eating behavior	Minimized intake of high FODMAP foods that are poorly digested, osmotically active, or highly fermented that can lead to symptoms Three phase diet with elimination, reintroduction, and personalization phases
Included/excluded	Focused exclusion of food items (eg, high lactose containing foods in the lactose-free diet)	Increased consumption of fruit, vegetables, whole grains, legumes, nuts, seeds, and heart healthy fats (olive and avocado; omega 3 from fish) Decreased consumption of red meats, processed foods, high sugar foods, and refined foods, and limited alcohol intake	Avoidance of foods rich in resistant starch, insoluble fiber, and sorbitol, carbonated drinks, alcohol, caffeine Limit fresh fruit to three servings/day Emphasis on fluid intake Eating habits: regular eating times, slow intake	Elimination of specific foods from high FODMAP groups: fructose, lactose, fructans, galactans, and polyols
Advantages	Less stringent to follow	Less restrictive, healthier relationship with food, and other cardiovascular health benefits	Healthier relationship with food Less stringent	Robust evidence to support use
Disadvantages	Only applicable in patients with specific food triggers	Less evidence specific to IBS	Can result in decreased fiber intake and deficiencies in micronutrients over time	Can result in decreased fiber intake and deficiencies in micronutrients, especially if left in elimination phase

*Lactose-free and gluten-free diets.
FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS=irritable bowel syndrome.

methylcellulose, oat bran, and the flesh of fruits and vegetables. Soluble fiber mixes with and holds water in the intestine, and can be categorized into viscous or non-viscous, short or long chain carbohydrates, and highly or minimally fermentable types. Short chained and highly fermentable fibers (eg, oligosaccharides) can trigger IBS symptoms through bacterial byproducts, but might also have beneficial effects as prebiotics.[7] Soluble fiber comes in many forms including powder, gummies, wafers, and capsules to improve palatability. All forms might have sugar, artificial sweeteners, and/or fillers that can contribute to bloating and osmotic diarrhea.

The most often recommended soluble fiber for IBS is psyllium, which is viscous and minimally fermentable. Psyllium holds water in the lumen of the intestine and improves colonic transit without worsening IBS symptoms, especially in those with IBS-C. Psyllium might benefit patients with IBS-D because of its viscosity, as its gel-forming nature may add bulk to stools and reduce urgency. A systematic review and meta-analysis of 14 randomized controlled trials (RCTs) involving 906 IBS patients found a significant benefit of fiber in global symptoms of IBS (RR=0.86; 95% CI 0.80 to 0.94, NNT=10; 95% confidence interval (CI) 6 to 33), though the benefit was only seen in soluble fiber (RR=0.83; 95% CI 0.73 to 0.94, NNT=7; 95% CI 4 to 25) and not with bran (insoluble fiber) (RR=0.90; 95% CI 0.79 to 1.03).[25] A more recent network meta-analysis of psyllium that included five RCTs and excluded two positive studies, however, found no benefit of psyllium over placebo (relative risk of failure to achieve global improvement 0.77 (0.58-1.02)), although only one of the included studies was considered low risk of bias.[26] In a double-blind crossover trial, addition of dietary fibers did not alter symptom response in patients with IBS treated with the low FODMAP diet but did augment stool bulk and normalize low stool water content and slow transit.[27]

On the basis of this evidence, most international guidelines recommend soluble but not insoluble fiber for the treatment of global IBS symptoms. The AGA suggests a fiber intake of about 25 to 35 grams per day[7] with slow increase to help prevent gas and bloating. Exceeding this goal is unlikely to improve and might worsen IBS symptoms.

Kiwifruit

Interest in both green and golden kiwifruit has arisen over the past few years from studies exploring the use of kiwifruit for the treatment of IBS-C. The first RCT compared two green kiwifruits per day with placebo capsules in IBS-C and healthy controls and found statistically significant decreases in colon transit time and increases in defecation frequency but no impact on pain.[28] A more recent international multicenter RCT randomized healthy controls (n=63), patients with functional constipation (n=60), and patients with IBS-C (n=61) to consume two green kiwifruits or psyllium (7.5 g) daily. Kiwifruit consumption was associated with a significant increase in weekly bowel movements (P=0.0003) and reduced gastrointestinal discomfort (P< 0.0001).

Although evidence to support the use of kiwifruit as a treatment modality is limited given the small sample sizes, it is an encouraging example of dietetics, using food as therapy. The intervention is relatively safe and accessible, but it is important to note that some people might be allergic to kiwifruit or develop an oral allergy syndrome owing to cross-reaction in those allergic to birch tree pollen. Individuals with latex allergy might be more likely to have an allergy to kiwifruit.

NICE dietary guidance

Dietary recommendations by NICE were first released in 2008 and updated in 2017, focusing on optimizing eating habits and lifestyle changes.[29] NICE guidance is less restrictive compared with many

other dietary recommendations for IBS and includes many suggestions for behaviors such as having regular meals, taking time to eat, avoiding missing meals, and getting adequate exercise and relaxation, in addition to dietary changes/restrictions (table 2). NICE guidance recommends the low FODMAP diet if symptoms do not improve.

Mediterranean diet

The traditional diet consumed in Mediterranean countries emphasizes minimally processed, plant based foods, nuts and healthy fats, and limited amounts of red meat and refined grains. Previous research has shown a reduced prevalence of disorder of gut-brain interaction in children and adolescents more adherent to a Mediterranean diet, but had not studied impact on existing IBS symptoms.[30 31] A six week unblinded RCT of a Mediterranean diet (n=29) versus habitual diet (n=30) found that a greater proportion of people in the Mediterranean diet group had reduced gastrointestinal symptoms (24/29, 83% *v* 11/30, 37%, P<0.001), as well as improved depression scores. No differences were seen between groups in FODMAP intake at week six, gastrointestinal adverse events, or microbiome parameters.[32] A cross-sectional, retrospective analysis of 106 patients with IBS and 109 healthy controls found that adherence to a Mediterranean diet was not associated with improved overall IBS symptoms, though certain pro- and anti-Mediterranean diet foods (table 2) were associated with more symptoms.[33] This diet has many overall benefits[23] but needs more evidence for use specifically in IBS.

Low FODMAP diet

The low FODMAP diet was first reported in a hypothesis paper in 2005, suggesting that reduction of certain fermentable short chain carbohydrates could improve symptoms of IBS by decreasing distention of the intestinal wall and reducing osmotically active compounds, thereby decreasing pain and diarrhea, respectively.[34] Other research has highlighted the potential of high FODMAP foods, in susceptible individuals, to alter the microbiome, increase lipopolysaccharides that disrupt and cross the intestinal epithelial barrier, and subsequently activate mast cells, causing pain and diarrhea.[35] The low FODMAP diet is delivered in three phases: elimination, reintroduction, and personalization.

The low FODMAP diet has been studied extensively as summarized in table 3. An older RCT comparing the low FODMAP with the modified NICE diet (mNICE) in IBS-D patients found no statistically significant difference in primary outcomes of adequate relief or composite outcome of pain and bowel movement changes.[36] In secondary outcomes, the low FODMAP diet group had more abdominal pain responders and lower pain, bloating, consistency, and urgency scores.[36] Post hoc analyses showed greater improvements in health related quality of life, anxiety, and activity impairment.[42] A 2022 systematic review of 13 RCTs showed superiority of low FODMAP diet to habitual diet and all other dietary interventions.[38] In primary care, an RCT showed superiority of the low FODMAP diet over antispasmodics as early as four weeks with results continuing at 16 week follow-up.[39] A single center, single-blind, three-arm RCT with 294 patients showed a higher proportion of those following four weeks of low FODMAP diet and NICE guidance achieved symptom improvement by IBS-SSS (irritable bowel syndrome symptom severity scale) over baseline compared with fiber optimized diet or optimized medical management. Adherence was over 90% in all groups with limited adverse events.[40]

Most low FODMAP diet studies have only assessed the elimination phase of the three phase treatment. One randomized crossover trial of 50 IBS patients showed that the elimination phase led to reduced symptom severity and improved quality of life which was sustained through re-introduction.[41]

Restrictive diets carry risks of dietary deficiencies over time. In the low FODMAP diet, studies have shown fiber intake decreases during elimination but normalized after re-introduction.[41] Post-hoc analysis of RCT data found both low FODMAP and mNICE diets resulted in decreased caloric intake, fewer daily meals, and fewer daily carbohydrates consumed. Patients on the low FODMAP diet had a decline in several micronutrients, but only riboflavin remained significantly decreased after correcting for calorie-adjusted nutrient intake. Fewer patients on the low FODMAP diet met the recommended intakes for thiamine and iron, and fewer in the mNICE met recommended intakes for calcium and copper.[43] Micronutrient deficiencies are more likely with longer time in the elimination phase, emphasizing the importance of a three-phase approach.

The recent AGA Clinical Practice Update on the use of diet for IBS highlighted the importance of the three phases of the low FODMAP diet. The elimination phase is intended to last four to six weeks and might be considered a diagnostic test to determine if and how much FODMAPs contribute to an individual's symptoms. If there is no improvement, then the prior diet should be resumed and other treatment options explored. Patients who respond to the elimination phase then enter the second, reintroduction, phase, during which foods from different high FODMAP groups are slowly added back to identify specific triggers. Careful monitoring of symptoms during this phase allows for development of the final, personalization phase where patients continue an individualized diet that maximizes diet variety and minimizes triggers. The guideline takes special care to recommend screening patients who are being considered for any elimination diet for eating disorders or disordered eating given the potential harm in this population.[7] The rising awareness of avoidant restrictive food intake disorder (ARFID) has highlighted that disordered eating is a spectrum, and what begins as food restriction to avoid symptoms might lead to mealtime anxiety or full blown eating disorders.[44]

Table 3 | Studies related to low FODMAP diet

Authors/study name	Design	Characteristics	Comparison	Outcomes	Limitations/comments
Elimination phase					
Eswaran SL, et al 2016[36]	RCT	84 patients with IBS-D	Low FODMAP diet versus modified NICE diet	Response at four weeks: No significant difference in proportion of patients who responded to treatment and used adequate relief (52% *v* 41%; P=0.31) No difference in composite endpoint of both ≥30% reduction in mean daily pain score and decrease in mean daily Bristol stool form of ≥1 compared with baseline (P=0.13)	Low FODMAP group had more: Abdominal pain responders (51% *v* 23%, P=0.008); reduction in average daily scores for abdominal pain, bloating, consistency, frequency, and urgency; improvements in health related quality of life, anxiety, and impairment of activities (post hoc analysis)[36] Deficiencies in micronutrients[37]: decrease in riboflavin from baseline adjusting for energy and nutrient intake (low FODMAP) Below recommended intakes of thiamine and iron (low FODMAP) and calcium and copper (modified NICE diet)
Black CJ, et al 2022[38]	Systematic review and meta-analysis	13 RCTs 994 patients	Low FODMAP versus habitual diet	Relative risk of symptoms not improving 0.67 (95% CI 0.48 to 0.91); P=0.99 Superior to all other interventions (including British Dietetic Association/NICE diets)	Tertiary or secondary care centers with support from registered dietitian
Carbone F, et al 2022[39]	RCT	459 patients in primary care	Low FODMAP diet versus antispasmodics	Response at eight weeks: 71% in diet group (155/218) *v* 61% in antispasmodic group (133/217); P=0.03	Difference observed at four weeks, which continued to week 16
Nybacka S, et al 2024[40]	Single center, single blind, three arm RCT	294 patients with moderate to severe IBS	Low FODMAP diet+NICE guidance (n=96) versus fiber optimized low carbohydrate diet (n=97) versus optimized medical treatment (n=101)	Response at four weeks: 76% of the low FODMAP group, 71% of the low carbohydrate group, and 58% of the optimized medical treatment group had reduction of >50 points on the IBS-SSS compared with baseline; significant between group differences (P=0.023)	Adherence: 95% of the low FODMAP group, 92% of the low carbohydrate group, and 90% of the optimized medical treatment group completed the trial No serious adverse events 5% of the optimized medical treatment group terminated early owing to side effects Two patients in each group discontinued owing to adverse events
Reintroduction phase					
Harvie RM, et al 2017[41]	Randomized crossover trial	50 patients with IBS	Group I: Elimination phase for three months, with reintroduction at three months Group II: Control for three months, with elimination phase beginning at three months	At three months: Group I *v* II: Reduction in IBS-SSS (275.6 (SD 63.6) to 128.8 (82.5) *v* 246.8 (71.1) to 203.6 (70.1); P<0.0002); increases in quality of life (68.5 (18.0) to 83 (13.4) *v* 72.9 (12.8) to 73.3 (14.4); P<0.0001); reduced IBS-SSS sustained at six months in group I	Fiber intake decreased during elimination but returned to normal after reintroduction
Response prediction					
Eswaran S, et al 2017[37]	Prospective cohort	38 patients with IBS	Four weeks of low FODMAP diet Prediction using baseline hydrogen breath test	55% of patients met the primary outcome (>30% improvement in bloating): AUC 0.69 (95% CI 0.51 to 0.86); P<0.05 Cut-off for hydrogen level 8 ppm: sensitivity 66.7%, specificity 82.4%	Significantly more patients who responded had baseline hydrogen levels >8 ppm versus patients who did not respond (66% *v* 17%, P<0.05) Baseline spot hydrogen level in patients who responded versus patients who did not respond: 9.5 (95% CI 3.3 to 17.3) *v* 4.5 (3.3 to 6.3); P<0.05

AUC=area under the curve; CI=confidence interval; FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS=irritable bowel syndrome; IBS-D=irritable bowel syndrome with diarrhea; IBS-SSS=irritable bowel syndrome symptom severity scale; NICE=National Institute for Health and Clinical Excellence; ppm=parts per million; RCT=randomized controlled trial; SD=standard deviation.

Given the costs (specialized foods, registered dietitian visits) and potential risks (micronutrient deficiencies, disordered eating) of a low FODMAP diet, researchers have sought to assess who is most likely to respond using baseline breath testing. A prospective cohort study using baseline hydrogen breath testing found an area under the curve for predicting low FODMAP diet response of 0.692 (95% CI 0.51 to 0.86, P<0.05) using a cutoff hydrogen level of 8 parts per million (sensitivity 66.7%, specificity 82.4).[45] Studies utilizing other lactose or fructose intolerance breath testing are lower quality with unclear utility in IBS.[46] Breath testing is not recommended by any guidelines for the prediction of response to the low FODMAP diet.

International guidelines generally support use of the low FODMAP diet with guidance from a registered dietitian, differing only in positioning of therapy **(**table 1**)**. Further studies are needed to predict who will respond to dietary intervention.

Dietary and herbal supplements

Glutamine

The essential amino acid L-glutamine, thought to help maintain intestinal integrity, was studied in an eight week, double-blind, randomized, placebo controlled trial of 54 patients with post-infectious IBS.[47] Symptom improvement by IBS-SSS was seen in 43/54 (79.6%) patients in the glutamine group and 3/52 (5.8%) of placebo (RR 63.8 95% CI 16.7 to 244.0; P<0.0001) with reduction in all secondary endpoints, including intestinal permeability, in the glutamine arm with no serious adverse events.

A RCT of 50 IBS patients from two gastroenterology clinics found that patients on low FODMAP diet plus 15 g/day of glutamine had statistically significant changes with improvement in IBS-SSS, satisfaction with bowel habits, and less interference with community function compared with low FODMAP diet alone.[48] Glutamine requires further study but might have an adjunctive role in certain patients.

Vitamin D

Vitamin D is a fat soluble vitamin with a primary role in the regulation of intestinal calcium/phosphate absorption and bone remodeling.[49] The utility of vitamin D in IBS is mixed. Low vitamin D concentrations have been linked to increased intestinal permeability, alterations of the microbiome, inflammation, mood disorders, and reduced quality of life[49] and deficiency has been associated with more severe IBS symptoms.[50] An RCT of 116 patients comparing vitamin D supplementation with placebo showed improvements in IBS-SSS, IBS-QOL (Quality Of Life questionnaire), and total symptom scores (P< 0.05) in patients receiving vitamin D[51] Another RCT of 74 people with IBS and vitamin D deficiency/insufficiency comparing vitamin D3 weekly versus placebo found significant improvements in IBS-SSS, and decrease in interleukin-6 values (P<0.01 and P=0.02, respectively).[52] However, two systematic reviews and meta-analyses from 2022 – one with four RCTs (n=335)[53] and the other with six RCTs (n=616)[54]—came to different conclusions. The first found that vitamin D is statistically significantly superior to placebo for the treatment of IBS and the second that it was associated with improvement in IBS-QOL but not IBS-SSS. Excess vitamin D supplementation can cause acute hypercalciuria and hypercalcemia, and chronic intoxication might lead to nephrocalcinosis, pain, and bone demineralization.[55] Given the potential risks and conflicting results in trials, vitamin D supplementation can be considered for short term trial treatment with careful monitoring for toxicities.

Microbiome based therapeutics

Prebiotics and probiotics

Interest in manipulation of the gastrointestinal microbiome for the purposes of health date back more than a century and included concepts such as “intestinal auto-intoxication” which was thought to drive aging and illness.[56] As alterations in the microbiome became linked to IBS, studies of probiotics for treatment increased and use became more common.[57 58] IBS, like many conditions, has broad patterns of microbial changes rather than a single microbiome signature, making hopes for precise, sustained microbiome manipulation to treat IBS an ongoing, unmet challenge and an area of active research.[59 60]

Probiotics

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.[61] A systematic review and meta-analysis of 53 RCTs (n=5545) found that probiotics had beneficial effects on global IBS symptoms and abdominal pain. It was not possible, however, to conclude which species, strains, or combinations of probiotics to recommend.[62] The 2020 AGA guideline for probiotic use across gastrointestinal disorders[8] reviewed 76 RCTs with 44 different probiotic strains or combinations used to treat IBS. It found statistically significant heterogeneity in study design, outcome, and probiotics used, and evidence for publication bias, leading to no recommendation for clinical use of probiotics in children and adults with IBS outside of clinical trials. The authors suggested stopping probiotics use owing to cost and limited evidence to suggest lack of harm. Although the US based AGA and ACG guidelines for treatment of IBS do not recommend probiotics, the British Society of Gastroenterology (BSG) guidelines for the treatment of IBS acknowledge evidence limitations but advise interested patients to pursue a time limited trial (12 weeks) and discontinue if no improvement (weak recommendation, very low quality of evidence) (table 1).[6]

Prebiotics

Prebiotics are substrates selectively used by host microorganisms to confer health benefits. A systematic review and meta-analysis of 11 RCTs (n=729) found no differences in overall responders, severity of abdominal pain, bloating and flatulence, quality of life, or adverse events.[63] The roles of prebiotics and probiotics in IBS is currently unclear.

Fecal microbiota transplant (FMT)

Given its success in microbiome restoration after infection with *Clostridium difficile*, FMT has been explored as a way of improving dysbiosis in IBS patients. A systematic review and meta-analysis of eight RCTs (n=472) found no statistically significant difference between the FMT and control groups for IBS symptom severity at any time point and that positive effects wear off over time with low success rates with attempted re-administration.[64] A systemic review, pairwise meta-analysis and network meta-analysis of seven RCTs (n=470) showed no advantage of FMT over placebo in pooled analyses but found FMT via duodenoscope and nasojejunal tube were superior to placebo in subgroup analyses.[65] The original efficacy study used a superdonor (a donor

whose stool results in significantly more successful FMT outcomes than other donors) and suggested that this plays a more important role in FMT for IBS than in FMT for recurrent *C difficile* infection.[66] Studies have shown that antibiotic pretreatment significantly reduces the engraftment of the FMT in patients with IBS-D[67] and that patients with more severe IBS had greater response rates compared with those who have moderate IBS in a post-hoc analysis of a prior randomized trial of FMT *v* placebo.[68]

From a safety standpoint, a review of more than 1000 patients who received FMT for *C. difficile* infections found the incidences of serious adverse events including death and infection to be 3.5% and 2.5%, respectively. A 2019 FDA safety alert reported two cases of invasive extended-spectrum beta-lactamase producing *Escherichia coli* in patients receiving FMT; one case, in a neutropenic patient post-bone marrow transplant, was fatal.[69] FMT was also linked to seven cases of Shiga toxin-producing *E coli*, which were undetected despite screening.[70] Recommended screening protocols for FMT donors are rigorous, involving questionnaires of general health and habits as well as extensive stool testing.[71]

FMT has not shown statistically significant benefit in IBS and carries risk of serious adverse events including infection. Multiple international guidelines currently do not recommend FMT for IBS treatment (table 1). However, given patient interest[72] and the role of dysbiosis in IBS, this remains an area of study as advancements in oral microbiome therapeutics progress.

Brain-gut behavior interventions

Brain-gut behavior therapies

Brain-gut behavior therapies (BGBTs) include classes of therapeutic approaches that incorporate techniques that directly target modifiable psychosocial and physiological processes that dysregulate the brain-gut axis (fig 2).[73 74] Cognitive behavioral therapy (CBT)[75] and gut directed hypnotherapy (GDH)[76] are the most evidence based BGBTs for IBS, both with durable treatment response after therapy completion.[77-79]Other emerging approaches include self-management training, mindfulness based stress reduction, psychodynamic-interpersonal therapy, and emotional awareness and processing approaches.[74 80] Factors such as anxiety and depression,[81] learned behaviors and early life adversity have been shown to impact stress sensitivity, which can disrupt brain-gut processing and negatively impact gastrointestinal related pain pathways, visceral hypersensitivity, and gastrointestinal motility.[82] When IBS symptoms become severe, this increases disease burden and hinders health related quality of life.[14] Brain-gut behavior therapies can address coping deficits,[83] reduce arousal, and improve self-regulation.[84] These approaches are particularly effective when integrated in gastroenterology practice settings and administered by mental health professionals specifically trained in psychogastroenterology.[84 85] ACG guidelines conditionally recommend that BGBTs can be used to treat global IBS symptoms for patients who do not have severe psychiatric comorbidities but this is based on low quality evidence.[9]

Cognitive behavioral therapy is a skills based approach that aims to target cognitive, affective, and behavioral processes, which trigger and/or exacerbate IBS symptoms. Skills training can incorporate a combination of relaxation strategies, cognitive restructuring, problem solving/emotion focused coping skills, exposure, and behavioral changes. Contextually based CBT approaches, such as acceptance and commitment therapy (ACT), are emerging BGBTs that incorporate techniques that target psychological flexibility and enhance

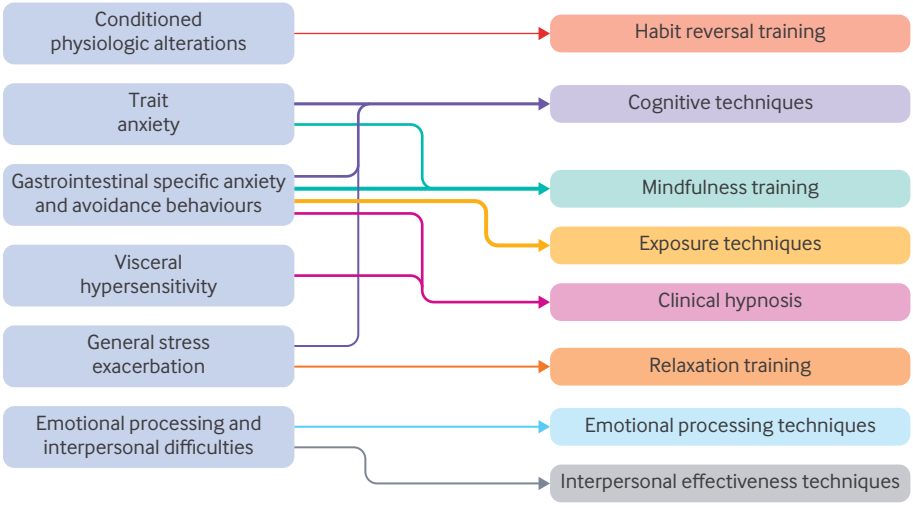

Fig 2 | Conceptual model of why and for whom brain–gut behavior therapies best work on the basis of hypothesized targets. Thicker lines represent greater evidence supporting target engagement for a technique. Adapted from Burton Murray H, Ljótsson B. Future of brain–gut behavior therapies: mediators and moderators *Gastroenterol Clin N Am* 2022;51:723-39

behaviors that align with a patient's values.[74] One quasi-experimental study of ACT showed improvement in depression and psychological capital in IBS patients.[86 87] Gut directed hypnosis, delivered over a set series of spaced sessions, involves a deep state of relaxation and focused attention that increases receptivity to suggestion. A recent systematic review and network meta-analysis of 41 RCTs (n=4072) found CBT (self-administered, minimal contact, or face to face) and GDH to be the most efficacious of several psychological therapies. In patients with refractory symptoms, CBT and GDH were more efficacious on a pooled relative risk of remaining symptomatic than education, support, or routine care controls in regard to their effect on IBS symptoms, but no single form of psychotherapy was superior to another.[88]

Self-management training programs target self-efficacy[74] and have been shown to have a positive impact on IBS health outcomes. For example, a systematic review and meta-analysis of 10 RCTs (n=886) demonstrated that compared with controls guided self-help interventions (GSH) for IBS had a medium effect size for the decrease in IBS symptom severity (SMD=0.72; 95% CI 0.34 to 1.08) and a large effect size for the increase in patient's quality of life (SMD=0.84; 95% CI 0.46 to 1.22).[89] Similarly, a systematic review of minimal contact psychological treatments for symptom management of IBS found that minimal contact interventions reduced IBS symptom severity and improved quality of life.[90] Mindfulness, a therapeutic technique involving conscious, judgment-free awareness of the present moment, has been shown to reduce IBS symptom severity and improve stress related outcomes in an RCT.[91] Psychodynamic-interpersonal therapy approaches aim to improve interpersonal functioning through the development of a collaborative patient-provider relationship[92] and have been shown to be effective in improving IBS symptoms (such as diarrhea and intermittent abdominal pain) in an RCT. Other emerging emotion focused interventions include emotional awareness training, which in RCT alongside symptom oriented medical treatment, was more effective at reducing abdominal pain in patients with IBS as compared with medical treatment alone.[93] Another RCT showed that written expressive disclosure, involving four brief writing sessions about deep thoughts and feelings about IBS, improved pain self-efficacy and reduced healthcare utilization compared with controls.[94] Similarly, a RCT of a brief, emotional awareness and expression therapy intervention that targeted emotional avoidance in patients with a history of trauma and emotional conflicts, reduced IBS symptom severity and improved quality of life in patients with IBS.[95] Other emerging transdiagnostic approaches that target emotional dysregulation from a CBT approach, including the Unified Protocol for Emotional Disorders, have been adapted for IBS, demonstrating a statistically significant decrease in depression, anxiety, stress, and gastrointestinal symptoms and statistically significant improvements in emotion regulation among patients with IBS, although larger RCTs are needed to confirm these findings.[96]

Despite robust evidence of benefit, widespread adoption of BGBTs has been limited by access, cost, provider expertise, time required, and patient related factors (eg, stigma). Traditionally, CBT is administered face to face in an individualized or group format, but advances in technology have allowed for development of minimal contact or self-administered delivery. This has prompted studies exploring alternative delivery mechanisms including in group sessions or in digital delivery. RCTs have shown benefit for group CBT compared with waitlist controls in drug refractory IBS,[97]and both group and individually nurse administered GDH were effective at improving IBS symptoms, psychological symptoms, and quality of life for patients with IBS.[98]

Digital delivery of psychologically based therapies

Digital therapeutics, which allow self-administration of therapeutic tools have been developed to increase access for BGBTs. Mahana IBS, an unguided web based CBT program which is no longer available, was the first FDA cleared digital therapeutic for IBS, and demonstrated promise for improving IBS symptom severity as well as psychological factors in pilot trials.[99] A subsequent multicenter RCT showed that two digital applications of CBT: telephone based CBT (TCBT) and web based Mahana IBS (WCBT) had statistically significant improvements in IBS symptom severity, quality of life, and mood, at 12 months. Compared with treatment as usual (TAU) (IBS-SSS=205.6) IBS symptoms were 61.6 (95% CI 33.8 to 89.5) points lower (P<0.001) in TCBT on the IBS-SSS and 35.2 (95% CI 12.6 to 57.8) points lower (P=0.002) in WCBT. Compared with TAU (Work and Social Adjustment Scale (WSAS) score=10.8), WSAS was 3.5 (95% CI 1.9 to 5.1) points lower (P<0.001) in TCBT and 3.0 (95% CI 1.3 to 4.6) points lower (P=0.001) in WCBT. Compared with TAU (mean Hospital Anxiety and Depression score=15.0 (SD=7.2), scores were an estimated 2.8 (95% CI 1.5 to 4.1) points lower (P<0.001) in the TCBT and 2.3 (95% CI 1.0 to 3.7) points lower (P=0.001) in the WCBT,[100] with sustained benefits at 24 months.[101] This provides further evidence for CBT as one of the most durable IBS treatment options. A similar CBT based app, Zemedy, has also been shown to significantly reduce IBS symptom severity and improve quality of life in the treatment group compared with a waitlist control group in a crossover RCT ($F_{1,79}$=20.49, P<0.001, Cohen d=1.01, and $F_{1,79}$=20.12, P<0.001, Cohen d=1.25, respectively).[102]

Digitally delivered GDH has also been developed. A retrospective evaluation of n=190 patients with self-reported IBS who completed Nerva, a GDH app, showed 64% responded positively, defined as a >30% reduction in abdominal pain.[103] An RCT of digital GDH delivered by another app, Regulora, showed 30.4% of patients met primary endpoint (abdominal pain response, defined as ≥ 30% reduction from

baseline in average daily abdominal pain intensity 4 weeks post treatment) but changes were not statistically significant over muscle relaxation control (P=0.5352).[104] Although an RCT (n=20) showed that web based hypnotherapy was slightly less effective than face-to-face treatment on the primary outcome (65% of subjects had a 50 point or more reduction in the IBS symptom severity score versus 76%, respectively), access to care was improved.[105] Overall, these alternative delivery methods improve patient access and allow additional care options with similar patient outcomes but evidence quality is still low.

Other complementary and integrative health approaches

Peppermint oil (*Mentha piperita*)

Peppermint oil has antispasmodic properties that have been well studied for the treatment of IBS and is suggested for relief of global IBS symptoms as a conditional recommendation in the ACG[9] as well as the BSG guidelines.[6] A recent systematic review and meta-analysis that included 10 RCTs (n=1030) found peppermint oil more efficacious than placebo for global IBS symptoms (RR of not improving=0.65; 95% CI 0.43 to 0.98, NNT=4) and abdominal pain (RR of not improving=0.76; 95% CI 0.62 to 0.93, NNT=7).[106] The peppermint oil group experienced more adverse events, which were predominantly mild symptoms of reflux, dyspepsia, and flatulence (RR of adverse event 1.57; 95% CI 1.04 to 2.37, NNH=14.5).[106] Patients should be counseled about GERD as a potential side effect.[6]

Cannabis (*Cannabis sativa*)

Cannabis sativa ("marijuana") is frequently used for recreational and medicinal purposes, with the first medicinal uses dating back to 4000 BC. The *C sativa* plant contains over 400 compounds, though the psychoactive cannabinoids, Δ-9 tetrahydrocannabinol (Δ-9-THC) and cannabidiol (CBD) are the best understood.[107] These interact with the body's endocannabinoid system, which consists of endogenous substrates, receptors, and enzymes for production and degradation of substrates.[108]

A small study using chewing gum containing 50 mg of CBD for the treatment of IBS found no difference in symptoms between treatment and placebo arms.[109] A database study of 31 272 patients ages 15 to 54 years of age admitted for IBS showed an increased risk (adjusted OR 1.41, 95% CI 1.32 to 1.50) of hospitalization in patients using cannabis compared with those not using it.[110] No studies of the whole cannabis plant on patients with IBS have been conducted at this time, in part owing to its controlled status in many parts of the world.

Several cannabis derivatives are being studied including dronabinol, a synthetic Δ-9-THC,[111-114] and olorinab, a highly selective peripherally acting cannabinoid 2 receptor agonist, both with no statistically significant benefits seen in IBS over placebo.[115] Therefore, despite increased access and patient interest, the risks of cannabis based treatments for IBS outweigh benefits based on current trials. Their use is not recommended in the Joint Consensus of Italian Societies guidelines.[10]

Traditional medicine practices

The Second Asian Consensus guidelines[12] suggests that traditional Chinese medicine could be helpful for some patients with moderate evidence based on a meta-analysis of 14 RCTs of traditional Chinese medicine in IBS-D patients with improvement of global IBS symptoms, abdominal pain, and diarrhea.[116] A formulation called Tongxie Yaofang has been studied the most among numerous formulations with 23 trials in 1972 IBS-D patients.[12] In a multicenter RCT of 1044 Chinese patients with IBS, Tongxie Yaofang was superior to placebo (79.3% responders *v* 31.9%) and similar to pinaverium (73.6% responders, chi squared >0.05) for treatment of abdominal pain.[117] A network meta-analysis showed non-inferiority between traditional Chinese medicine and antispasmodics in global IBS symptom relief.[118]

Other ancient herbal medicine practices with evidence in IBS include Ayurvedic medicine,[119] and Japanese Kampo agents including rikkunshito and keishikashakuyakuto.[120] The Second Asian Consensus suggests Kampo could be considered effective with low grade evidence.[12] More data are needed to recommend these formulations in global populations.

Other herbal formulations

There are numerous herbals and supplements used by patients for the treatment of IBS, some of which have been studied in literature. These include curcumin, fennel,[121] turmeric,[122] caraway oil,[123] melatonin,[124] aloe,[125] ginger,[126] berberine hydrochloride,[127] and mixed agents such as STW5, which has shown efficacy in functional dyspepsia.[128 129]

Acupuncture

Acupuncture, a Chinese technique dating back more than 2000 years,[130] utilizes the insertion of thin needles into specified acupoints along 12 energy channels ("meridians") to balance the flow of energy throughout the body. This technique has been studied in animal and human models of IBS with the goal of improving inflammation, visceral hypersensitivity, and central sensitization through change in functional connections, regulation of gut motility,[131 132] modulation of serotonin response,[133] and downregulating overexpression of substance P and vasoactive intestinal peptide in IBS-C populations.[134 135]

A 2006 Cochrane review[136] comprising six individual trials, found acupuncture was not superior to sham acupuncture (RR 1.28 (95% CI 0.83 to 1.98, n=106), but was superior to herbal medications (RR 1.14, 95% CI 1.00 to 1.31, n=132) and as an addition to psychotherapy compared with psychotherapy alone (RR 1.21 (95% CI 1.03 to 1.39,

n=100). The overall quality of the trials, however, was low with significant heterogeneity, preventing conclusive assessment. Since then, multiple studies and meta-analyses have been conducted trying to clarify the benefit of acupuncture in IBS. A 2014 meta-analysis[137] of six RCTs (2000-2012), one with positive and five with no benefit in IBS, found a pooled benefit to acupuncture (OR 1.75(1.24 to 2.46)). Updated meta-analyses suggest acupuncture and sham acupuncture both performed better than drugs (including alosetron and rifaximin) with fewer side effects[138 139] with combination of acupuncture and medicines having higher benefit than acupuncture alone.[139 140] Impact was greater in IBS-D compared with all subtypes,[138] and short term acupuncture treatment showed durable impact at 12 months, but not at 24 month follow-up.[141] Overall, the quality of evidence supporting acupuncture remains low[142] with no statistically significant differentiation between true and sham acupuncture.[143]

One challenge of evaluating the utility of acupuncture is heterogeneity in acupoints selected, which can vary depending on individual patient symptoms or vary between studies in similar patient populations. This led to a Delphi expert consensus group to establish acupuncture best practices to standardize treatment.[144] In addition, sham acupuncture in trials is sometimes performed with blunt needling at the same acupoints as true acupuncture, effectively delivering acupressure, which has shown benefit on its own for symptom treatment,[145 146] bringing into question whether this is a true control.

Given this evidence, the utility of acupuncture remains unclear with a possible positive effect and low risk for adverse events. Studies suggest acupuncture might have a role as an adjunctive therapy to medications or psychotherapy with 12 month durability.[141] Due to lack of benefit over sham, the Canadian Association of Gastroenterology guidelines do not recommend offering acupuncture for global IBS symptoms[13]; no mention is made in other guidelines thus far.

Electroacupuncture

Electroacupuncture is an emerging therapy that involves the use of small electric currents applied to acupuncture needles with the aim of enhancing the therapeutic effect of acupuncture. A RCT of 96 functional constipation patients in China compared electroacupuncture with mosapride with the electroacupuncture group showing improved weekly spontaneous bowel movements, stool consistency and ease of defecation with partial improvement in quality of life.[147] A single blinded randomized trial of electroacupuncture versus sham in women with constipation suggests that treatment with electroacupuncture enhances parasympathetic nervous system activity as measured by heart rate variability.[148] The role of electroacupuncture in treatment of IBS remains unclear but holds promise given improvement in other constipation subtypes.

Mind-body interventions

Mind-body interventions, a complementary and integrative health approach, target "interactions among the brain, mind, body, and behavior, with the intent to use the mind to affect physical functioning and promote health."[149] Mind-body interventions utilized for IBS therapy include general exercise, yoga and tai-chi or qi-gong.

Exercise

Exercise in general has been shown to improve IBS symptoms through a variety of mechanisms with potential long term durability (>5 years).[150] Low to moderate intensity aerobic exercise was shown in a RCT of 109 women to attenuate inflammation and signs of oxidative stress correlating with improvements in IBS symptoms.[151] In patients with cognitive bias or poor coping styles, exercise combined with CBT seems to improve IBS symptom scores as well as coping and cognitive bias.[152] A systematic review of 14 RCTs (n=683) showed statistically significant benefit for patients with IBS across a variety of aerobic and static activity, but studies had significant bias.[153] A Cochrane review (11 RCTs, n=622) of physical activity including yoga, treadmill exercise, or generalized support to increase physical activity for the treatment of IBS concluded that physical activity might improve symptoms but not quality of life or abdominal pain with the quality of evidence deemed very low.[154] The BSG guidelines strongly recommend regular exercise as a first line treatment for global IBS symptoms (weak quality evidence).[6]

Meditative movement (yoga/qi-gong)

Meditative movement practices, which combine postures/movements with meditation practice, can be used for stress sensitive disorders such as IBS. Yoga, originating in India, is among the most popularized meditative movement practice and involves three main components: asanas (physical postures), pranayama (breathwork), and dyhana (meditation). Yoga is hypothesized to correct parasympathetic underactivity in stress related disorders,[155] and modulate stress induced immune responses,[156] which improve IBS symptoms. Other forms of meditative movement include qi-gong and its martial arts form, tai-chi, both of which were developed in China thousands of years ago. Both involve postures and gentle movements conducted with mental focus, meditation, and breathing strategies to promote relaxation.

A systematic review of six RCTs of yoga for IBS found yoga to be more beneficial than conventional care, with statistically significant decreases in bowel symptoms, IBS symptom severity, and anxiety with improvements in quality of life, global symptoms, and physical functioning. No statistically significant differences were found between yoga and exercise, suggesting yoga to be equally effective as other movement practices. Yoga was concluded to be safe and feasible, with no adverse events in studies that reported safety data.[157] Studies were deemed

heterogeneous and had methodologic limitations, limiting generalizability and interpretation of implications. In line with increasing interest in digital health, virtual yoga programs were also shown in RCTs to be safe and feasible, with positive impacts on IBS symptom severity from baseline to follow-up in the yoga group but not in the advice only control group. There were no statistically significant differences between groups in symptom severity, but statistically significant improvements were seen for quality of life, fatigue, and perceived stress in the yoga group compared with control.[158]

From the success of yoga, other meditative movement therapies have emerged for treatment of IBS including tai-chi, and qi-gong. A virtual tai chi program was piloted for IBS-C patients in one single-arm trial and was found to be feasible with high satisfaction among completers, and statistically significant improvement in symptom severity from baseline to follow-up. Secondary outcomes were positive including improvements in other IBS symptom scoring measures, IBS related quality of life, measured abdominal diameter, and leg strength.[159] Further studies are needed to draw conclusions.

Meditative movement might have benefit compared with other forms of meditation for this population because, in addition to increased activity, it downregulates the central nervous system, which challenges stagnation and arousal, both of which are potential factors in gastrointestinal dysregulation. Although many informal resources exist, further empirical research is needed to understand clinical utility

Physical/manual manipulations and biofeedback

Physical therapy, including manual manipulations, myofascial release, pelvic floor rehabilitation and biofeedback, have an important role in management of musculoskeletal and myofascial pain conditions, many of which are comorbid with IBS.

A 2014 systematic review evaluated five studies (n=204) utilizing osteopathic manipulation for IBS, finding pronounced short term benefits in IBS symptoms compared with sham or standard of care.[160] Like acupuncture, studies of osteopathic manipulation utilize varied, individualized approaches, and lack standardized symptom severity or secondary outcome measures,[160] making findings difficult to generalize and interpret. Except for a small RCT on micro-physiotherapy which showed improvement in IBS over sham,[161] other manual therapies have evidence in comorbid pain conditions such as fibromyalgia[162] but not in IBS.

A Cochrane Review of RCTs (n=300) assessed multiple biofeedback mechanisms including thermal (skin temperature, four trials), rectosigmoid (rectal manometry/barostat, one trial) , heart rate variability (pulse oximetry, two trials), and electrocutaneous biofeedback (two trials), all aimed at helping patients control their bodily processes (eg, heart rate, breathing) with the goal of modulating response. This review found high or unclear risk of bias in all studies with overall uncertain benefit of biofeedback for IBS symptoms.[163] Further studies are required to understand which modality has benefit in IBS treatment.

Other emerging therapies

Polymethylsiloxane polyhydrate

Polymethylsiloxane polyhydrate (Enterosgel) is an orally consumed intestinal adsorbent that is classified as a medical device with no pharmacological action. Enterosgel was shown in vitro to bind bacterial toxins, endogenous and exogenous substances, immune proteins, and bile acids.[164] In a RCT of 105 primary care patients with acute diarrhea, the Enterosgel group had shortened duration of diarrhea compared with the control (27 hours *v* 39 hours, HR 1.74 (95% CI 1.06 to 2.87), P=0.03) with no adverse events.[165] A multicenter RCT of 440 patients with IBS-D showed that Enterosgel performed better than placebo in the composite primary outcome of pain reduction and stool consistency score (37.4% vs 24.3% (OR 1.95, NNT=8, P=0.002) and decreased stool urgency and frequency. Sixty per cent of patients reported adequate relief of symptoms with no increase in adverse events.[166] This over-the-counter therapeutic can be considered for treatment of IBS-D and warrants further investigation.

Vagal nerve stimulation

Auricular nerve stimulation utilizes electrocutaneous stimulation at the auricular branch of the vagal nerve to achieve vagal nerve modulation, potentially impacting gut barrier function and inflammatory response to improve visceral hypersensitivity.[167 168] Trials have shown improvement in quality of life and IBS pain scores as well as number of spontaneous bowel movements in an IBS-C cohort.[169]

A percutaneous auricular nerve stimulator (IB-STIM) has received FDA clearance for use in adolescents with functional abdominal pain related disorder of gut-brain interactions on the basis of a randomized, sham controlled trial (n=115): 81% of the treatment group (versus 26% of sham group) showed global symptom improvement after three weeks of treatment with greater reduction of worst pain scores compared with sham (P<0·0001). The effect was sustained at 12 weeks follow-up. Side effects included ear discomfort, adhesive allergy, and syncope.[170] This product is not yet available for adult IBS populations.

Vibrating capsule

An ingestible vibrating capsule (VIBRANT) has been approved for treatment of chronic idiopathic constipation (CIC) based on study data showing improvement in number of complete spontaneous bowel movements, straining, stool consistency, and quality of life compared with placebo capsule[171] with similar results in a functional constipation population.[172] Early evaluation of this capsule in patients with IBS-C and chronic constipation did not

show statistically significant improvement in overall colonic transit compared with sham but at least 25% of the patients experienced increase in colonic transit speed.[173] The utility of the vibrating capsule for IBS-C treatment requires further study.

Virtual reality

The use of virtual reality as a therapeutic tool has been studied over the past decade, with benefit in management of acute and chronic pain through proposed mechanisms of distraction, decreased sensitization, and management of symptom driven mood disturbance.[174] Virtual reality for IBS treatment is being studied with programming specifically targeted to gut directed causes of pain, combining educational content, CBT techniques, and exposure therapies within an immersive virtual environment. Early studies show patient acceptance of the treatment modality with further studies on efficacy and mechanism of action currently under way.[175]

Guidelines

Table 1 contains a summary of international guidelines for non-pharmaceutical interventions in IBS.

Conclusion

Treatment of IBS has evolved over the past two decades with more options and evidence for non-pharmaceutical treatments (fig 3). International guidelines support the use of diet based interventions as front line therapy from increased soluble fiber to more general dietary changes (eg, NICE guidance, low-FODMAP diet). Guidelines overall support psychological and behavior based interventions with caveats to patient selection and differing suggestions for where these should be positioned. complementary and integrative health therapies including peppermint oil and traditional herbal based interventions are gaining acceptance with mixed recommendations in guidelines. Microbiome based therapies are similar with overall limited evidence and mixed support from guidelines for probiotic use and consensus that FMT is not currently recommended for IBS treatment. Continued areas of research and development blend traditional and modern techniques and include electroacupuncture, percutaneous vagal nerve stimulators, intestinal binders, vibrating capsules, digitally delivered psychotherapies, and virtual reality.

IBS is a heterogeneous disorder and many of the non-pharmaceutical approaches aim to provide personalized therapy for patients within a standardized framework, leading to challenges in standardizing and interpreting research for many of these interventions. Future research directions for many of these options should include identifying optimal protocols/dosages and treatment durations.

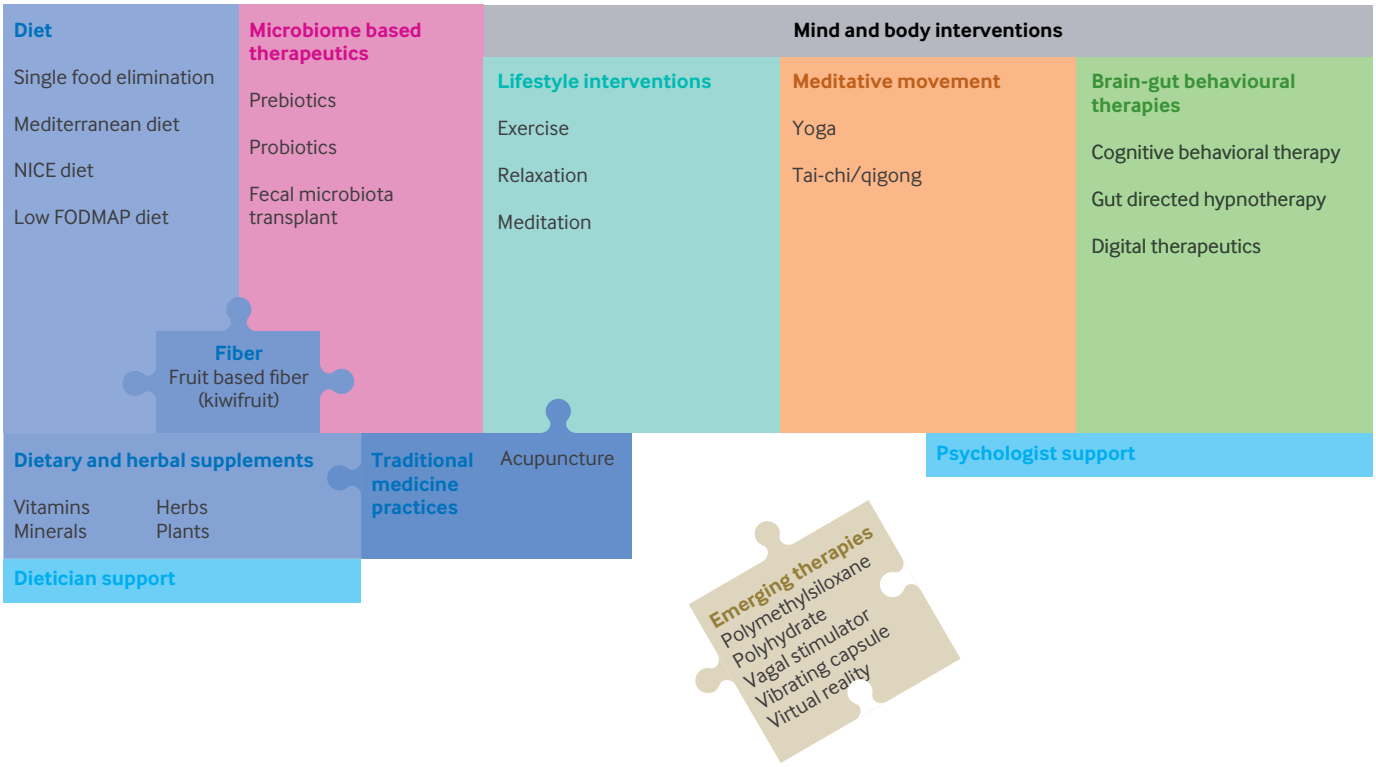

Fig 3 | Irritable bowel syndrome is a multifactorial illness and should be approached in a multidisciplinary manner with a complement of therapeutic modalities to address that patient's individual symptom phenotype. Therapeutic options include pharmacologic (drug) options, complementary and more "natural" products, diet based interventions, and those focused on mind-body interventions, spanning the spectrum of cognitively focused to more movement focused. Emerging therapies with devices and more invasive interventions can also have a role in treatment. Adapted from National Center for Complementary and Integrative Health. Complementary, Alternative, or Integrative Health: What's In a Name? https://www.nccih.nih.gov/health/complementary-alternative-or-integrative-health-whats-in-a-name

QUESTIONS FOR FUTURE RESEARCH

Research questions

- How do we standardize delivery of non-pharmaceutical therapeutics to better assess efficacy and effectiveness?
- What is the cross cultural applicability of culturally rooted therapies from the culture of origin to a global population?
- What is the role of digital therapeutics in improving care delivery and access?
- How can we optimize implementation of evidence based non-pharmaceutical modalities in real world settings?

PATIENT INVOLVEMENT

We utilized patient input from clinical practice to include complementary and alternative therapies that are frequently explored or utilized from a patient standpoint. After drafting the paper, we involved well known patient advocates within the IBS space to review the paper to ensure all relevant and evidence based therapies were covered within the review.

Patient advocates Johannah Ruddy, president of Gastro Consulting and Communications, director of patient advocacy for Ardelyx, co-founder of Tuesday Night IBS, author of multiple books on patient centered communication in IBS, former chief operating officer and executive director of the Rome Foundation, Ceciel Rooker, president and executive director of the International Foundation for Gastrointestinal Disorders, an IBS patient advocate group, and Jeffrey Roberts, founder of IBS Patient Support Group and cofounder of Tuesday Night IBS, reviewed the paper and gave feedback which was incorporated into the final manuscript.

As the armamentarium for IBS treatment expands with increasingly refined options, we can offer growing hope for both patients and providers.

We thank Ceciel Rooker, Jeffrey Roberts, Johannah Ruddy, and Michael Camilleri for their time and input to enhance the quality of this review.

Contributors: XJW, ET, and JS all contributed to initial planning, literature search, article review, article selection, and drafting of the manuscript. Authors all contributed to revisions and the final product was reviewed and approved by all authors before submission. XJW is the guarantor.

Competing interests: The authors have no relevant conflicts of interest for disclosure.

Provenance and peer review: Commissioned; externally peer reviewed.

1 Rangan V, Ballou S, Shin A, Camilleri M, Lembo A, Beth Israel Deaconess Medical Center GI Motility Working Group. Use of treatments for irritable bowel syndrome and patient satisfaction based on the IBS in America survey. *Gastroenterology* 2020;158:786-788.e1.
2 Astin JA. Why patients use alternative medicine: results of a national study. *JAMA* 1998;279:1548-53.
3 Eisenberg DM, Kessler RC, Van Rompay MI, et al, Perceptions about complementary therapies relative to conventional therapies among adults who use both: results from a national survey. *Ann Intern Med* 2001;135:344-51.
4 Lembo A, Sultan S, Chang L, Heidelbaugh JJ, Smalley W, Verne GN. AGA Clinical practice guideline on the pharmacological management of irritable bowel syndrome with diarrhea. *Gastroenterology* 2022;163:137-51.
5 Chang L, Sultan S, Lembo A, Verne GN, Smalley W, Heidelbaugh JJ. AGA Clinical practice guideline on the pharmacological management of irritable bowel syndrome with constipation. *Gastroenterology* 2022;163:118-36.
6 Vasant DH, Paine PA, Black CJ, et al, British Society of Gastroenterology guidelines on the management of irritable bowel syndrome. *Gut* 2021;70:1214-40.
7 Chey WD, Hashash JG, Manning L, Chang L. AGA clinical practice update on the role of diet in irritable bowel syndrome: expert review. *Gastroenterology* 2022;162:1737-1745.e5.
8 Su GL, Ko CW, Bercik P, et al, AGA Clinical Practice Guidelines on the role of probiotics in the management of gastrointestinal disorders. *Gastroenterology* 2020;159:697-705.
9 Lacy BE, Pimentel M, Brenner DM, et al, ACG clinical guideline: management of irritable bowel syndrome. *Am J Gastroenterol* 2021;116:17-44.
10 Barbara G, Cremon C, Bellini M, et al, Italian guidelines for the management of irritable bowel syndrome: Joint Consensus from the Italian Societies of: Gastroenterology and Endoscopy (SIGE), Neurogastroenterology and Motility (SINGEM), Hospital Gastroenterologists and Endoscopists (AIGO), Digestive Endoscopy (SIED), General Medicine (SIMG), Gastroenterology, Hepatology and Pediatric Nutrition (SIGENP) and Pediatrics (SIP). *Dig Liver Dis* 2023;55:187-207.
11 Ghoshal UC, Sachdeva S, Pratap N, et al, Indian consensus statements on irritable bowel syndrome in adults: A guideline by the Indian Neurogastroenterology and Motility Association and jointly supported by the Indian Society of Gastroenterology. *Indian J Gastroenterol* 2023;42:249-73.
12 Gwee KA, Gonlachanvit S, Ghoshal UC, et al, Second Asian consensus on irritable bowel syndrome. *J Neurogastroenterol Motil* 2019;25:343-62.
13 Moayyedi P, Andrews CN, MacQueen G, et al, Canadian Association of Gastroenterology clinical practice guideline for the management of irritable bowel syndrome (IBS). *J Can Assoc Gastroenterol* 2019;2:6-29.
14 Sperber AD, Bangdiwala SI, Drossman DA, et al, Worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome Foundation Global Study. *Gastroenterology* 2021;160:99-114.e3.
15 Staller K, Olén O, Söderling J, et al, Mortality risk in irritable bowel syndrome: results from a nationwide prospective cohort study. *Am J Gastroenterol* 2020;115:746-55.
16 Ballou S, McMahon C, Lee HN, et al, Effects of irritable bowel syndrome on daily activities vary among subtypes based on results from the IBS in America survey. *Clin Gastroenterol Hepatol* 2019;17:2471-2478.e3.
17 Canavan C, West J, Card T. Review article: the economic impact of the irritable bowel syndrome. *Aliment Pharmacol Ther* 2014;40:1023-34.
18 Bosman MHMA, Weerts ZZRM, Snijkers JTW, et al, The socioeconomic impact of irritable bowel syndrome: an analysis of direct and indirect health care costs. *Clin Gastroenterol Hepatol* 2023;21:2660-9.
19 Shah ED, Chang L, Salwen-Deremer JK, et al, Contrasting clinician and insurer perspectives to managing irritable bowel syndrome: multilevel modeling analysis. *Am J Gastroenterol* 2021;116:748-57.
20 Shah ED, Salwen-Deremer JK, Gibson PR, Muir JG, Eswaran S, Chey WD. Comparing costs and outcomes of treatments for irritable bowel syndrome with diarrhea: cost-benefit analysis. *Clin Gastroenterol Hepatol* 2022;20:136-144.e31.
21 Böhn L, Störsrud S, Törnblom H, Bengtsson U, Simrén M. Self-reported food-related gastrointestinal symptoms in IBS are common and associated with more severe symptoms and reduced quality of life. *Am J Gastroenterol* 2013;108:634-41.
22 Lenhart A, Ferch C, Shaw M, Chey WD. Use of dietary management in irritable bowel syndrome: results of a survey of over 1500 United States gastroenterologists. *J Neurogastroenterol Motil* 2018;24:437-51.
23 Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. *BMJ* 2008;337:a1344.
24 El-Salhy M, Hausken T, Gilja OH, Hatlebakk JG. The possible role of gastrointestinal endocrine cells in the pathophysiology of irritable bowel syndrome. *Expert Rev Gastroenterol Hepatol* 2017;11:139-48.
25 Moayyedi P, Quigley EM, Lacy BE, et al, The effect of fiber supplementation on irritable bowel syndrome: a systematic review and meta-analysis. *Am J Gastroenterol* 2014;109:1367-74.
26 Black CJ, Yuan Y, Selinger CP, 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.

27 So D, Yao CK, Ardalan ZS, et al, Supplementing dietary fibers with a low FODMAP diet in irritable bowel syndrome: a randomized controlled crossover trial. *Clin Gastroenterol Hepatol* 2022;20:2112-2120.e7.
28 Chang CC, Lin YT, Lu YT, Liu YS, Liu JF. Kiwifruit improves bowel function in patients with irritable bowel syndrome with constipation. *Asia Pac J Clin Nutr* 2010;19:451-7.
29 National Institute of Health and Care Excellence. Irritable bowel syndrome in adults: diagnosis and management. 2017.
30 Zito FP, Polese B, Vozzella L, et al, Good adherence to Mediterranean diet can prevent gastrointestinal symptoms: A survey from Southern Italy. *World J Gastrointest Pharmacol Ther* 2016;7:564-71.
31 Agakidis C, Kotzakioulafi E, Petridis D, Apostolidou K, Karagiozoglou-Lampoudi T. Mediterranean diet adherence is associated with lower prevalence of functional gastrointestinal disorders in children and adolescents. *Nutrients* 2019;11:1283.
32 Staudacher HM, Mahoney S, Canale K, et al, Clinical trial: a Mediterranean diet is feasible and improves gastrointestinal and psychological symptoms in irritable bowel syndrome. *Aliment Pharmacol Ther* 2024;59:492-503.
33 Chen EY, Mahurkar-Joshi S, Liu C, et al, The association between a Mediterranean diet and symptoms of irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2024;22:164-172.e6.
34 Gibson PR, Shepherd SJ. Personal view: food for thought—western lifestyle and susceptibility to Crohn's disease. The FODMAP hypothesis. *Aliment Pharmacol Ther* 2005;21:1399-409.
35 Singh P, Grabauskas G, Zhou SY, Gao J, Zhang Y, Owyang C. High FODMAP diet causes barrier loss via lipopolysaccharide-mediated mast cell activation. *JCI Insight* 2021;6:e146529.
36 Eswaran SL, Chey WD, Han-Markey T, Ball S, Jackson K. A randomized controlled trial comparing the low FODMAP diet *v* modified NICE guidelines in US adults with IBS-D. *Am J Gastroenterol* 2016;111:1824-32.
37 Eswaran S, Farida JP, Green J, Miller JD, Chey WD. Nutrition in the management of gastrointestinal diseases and disorders: the evidence for the low FODMAP diet. *Curr Opin Pharmacol* 2017;37:151-7.
38 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.
39 Carbone F, Van den Houte K, Besard L, et al, DOMINO Study CollaboratorsDomino Study Collaborators. 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.
40 Nybacka S, Törnblom H, Josefsson A, et al, A low FODMAP diet plus traditional dietary advice versus a low-carbohydrate diet versus pharmacological treatment in irritable bowel syndrome (CARIBS): a single-centre, single-blind, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2024;9:507-20.
41 Harvie RM, Chisholm AW, Bisanz JE, et al, Long-term irritable bowel syndrome symptom control with reintroduction of selected FODMAPs. *World J Gastroenterol* 2017;23:4632-43.
42 Eswaran S, Chey WD, Jackson K, Pillai S, Chey SW, Han-Markey T. A diet low in fermentable oligo-, di-, and monosaccharides and polyols improves quality of life and reduces activity impairment in patients with irritable bowel syndrome and diarrhea. *Clin Gastroenterol Hepatol* 2017;15:1890-1899.e3.
43 Eswaran S, Dolan RD, Ball SC, Jackson K, Chey W. The impact of a 4-week low-FODMAP and mNICE diet on nutrient intake in a sample of US adults with irritable bowel syndrome with diarrhea. *J Acad Nutr Diet* 2020;120:641-9.
44 Burton Murray H, Staller K. When food moves from friend to foe: why avoidant/restrictive food intake matters in irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2022;20:1223-5.
45 Somvanapanich P, Pitisuttithum P, Sirimongkolkasem J, et al, Spot hydrogen breath test for predicting response to low fermentable oligo-, di-, mono-saccharides, and polyols dietary advice in patients with bloating. *J Neurogastroenterol Motil* 2023;29:513-9.
46 Wilder-Smith CH, Olesen SS, Materna A, Drewes AM. Predictors of response to a low-FODMAP diet in patients with functional gastrointestinal disorders and lactose or fructose intolerance. *Aliment Pharmacol Ther* 2017;45:1094-106.
47 Zhou Q, Verne ML, Fields JZ, et al, Randomised placebo-controlled trial of dietary glutamine supplements for postinfectious irritable bowel syndrome. *Gut* 2019;68:996-1002.
48 Rastgoo S, Ebrahimi-Daryani N, Agah S, et al, Glutamine Supplementation Enhances the Effects of a Low FODMAP Diet in Irritable Bowel Syndrome Management. *Front Nutr* 2021;8:746703.
49 Barbalho SM, Goulart RA, Araújo AC, Guiguer ÉL, Bechara MD. Irritable bowel syndrome: a review of the general aspects and the potential role of vitamin D. *Expert Rev Gastroenterol Hepatol* 2019;13:345-59.
50 Abbasnezhad A, Amani R, Hajiani E, Alavinejad P, Cheraghian B, Ghadiri A. Effect of vitamin D on gastrointestinal symptoms and health-related quality of life in irritable bowel syndrome patients: a randomized double-blind clinical trial. *Neurogastroenterol Motil* 2016;28:1533-44.
51 Jalili M, Vahedi H, Poustchi H, Hekmatdoost A. Effects of vitamin D supplementation in patients with irritable bowel syndrome: a randomized, double-blind, placebo-controlled clinical trial. *Int J Prev Med* 2019;10:16.
52 Khalighi Sikaroudi M, Mokhtare M, Janani L, et al, Vitamin D3 supplementation in diarrhea-predominant irritable bowel syndrome patients: the effects on symptoms improvement, serum corticotropin-releasing hormone, and interleukin-6 —a randomized clinical trial. *Complement Med Res* 2020;27:302-9.
53 Huang H, Lu L, Chen Y, Zeng Y, Xu C. The efficacy of vitamin D supplementation for irritable bowel syndrome: a systematic review with meta-analysis. *Nutr J* 2022;21:24.
54 Abuelazm M, Muhammad S, Gamal M, et al, The effect of vitamin D supplementation on the severity of symptoms and the quality of life in irritable bowel syndrome patients: a systematic review and meta-analysis of randomized controlled trials. *Nutrients* 2022;14:2618.
55 Pludowski P, Holick MF, Grant WB, et al, Vitamin D supplementation guidelines. *J Steroid Biochem Mol Biol* 2018;175:125-35.
56 Mathias M. Autointoxication and historical precursors of the microbiome-gut-brain axis. *Microb Ecol Health Dis* 2018;29:1548249.
57 Barbara G, Stanghellini V, Cremon C, et al, Probiotics and irritable bowel syndrome: rationale and clinical evidence for their use. *J Clin Gastroenterol* 2008;42(Suppl 3 Pt 2):S214-7.
58 Quigley EM. Probiotics in irritable bowel syndrome: the science and the evidence. *J Clin Gastroenterol* 2015;49(Suppl 1):S60-4.
59 Wensel CR, Pluznick JL, Salzberg SL, Sears CL. Next-generation sequencing: insights to advance clinical investigations of the microbiome. *J Clin Invest* 2022;132:e154944.
60 Ng QX, Yau CE, Yaow CYL, et al, What has longitudinal "Omics" studies taught us about irritable bowel syndrome? A systematic review. *Metabolites* 2023;13:484.
61 Hill C, Guarner F, Reid G, 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.
62 Zhang T, Zhang C, Zhang J, Sun F, Duan L. Efficacy of probiotics for irritable bowel syndrome: a systematic review and network meta-analysis. *Front Cell Infect Microbiol* 2022;12:859967.
63 Wilson B, Rossi M, Dimidi E, Whelan K. Prebiotics in irritable bowel syndrome and other functional bowel disorders in adults: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2019;109:1098-111.
64 Abdelghafar YA, AbdelQadir YH, Motawea KR, et al, Efficacy and safety of fecal microbiota transplant in irritable bowel syndrome: An update based on meta-analysis of randomized control trials. *Health Sci Rep* 2022;5:e814.
65 Rokkas T, Hold GL. A systematic review, pairwise meta-analysis and network meta-analysis of randomized controlled trials exploring the role of fecal microbiota transplantation in irritable bowel syndrome. *Eur J Gastroenterol Hepatol* 2023;35:471-9.
66 El-Salhy M, Hatlebakk JG, Gilja OH, Bråthen Kristoffersen A, Hausken T. Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome in a randomised, double-blind, placebo-controlled study. *Gut* 2020;69:859-67.
67 Singh P, Alm EJ, Kelley JM, et al, Effect of antibiotic pretreatment on bacterial engraftment after Fecal Microbiota Transplant (FMT) in IBS-D. *Gut Microbes* 2022;14:2020067.
68 El-Salhy M, Mazzawi T, Hausken T, Hatlebakk JG. The fecal microbiota transplantation response differs between patients with severe and moderate irritable bowel symptoms. *Scand J Gastroenterol* 2022;57:1036-45.
69 DeFilipp Z, Bloom PP, Torres Soto M, et al, Drug-Resistant *E. coli* bacteremia transmitted by fecal microbiota transplant. *N Engl J Med* 2019;381:2043-50.
70 Zellmer C, Sater MRA, Huntley MH, Osman M, Olesen SW, Ramakrishna B. Shiga toxin-producing *Escherichia coli* transmission via fecal microbiota transplant. *Clin Infect Dis* 2021;72:e876-80.
71 Ng RW, et al, Revisiting the donor screening protocol of faecal microbiota transplantation (FMT): a systematic review. *Gut* 2023.
72 Ekekezie C, Perler BK, Wexler A, Duff C, Lillis CJ, Kelly CR. Understanding the Scope of Do-It-Yourself Fecal Microbiota Transplant. *Am J Gastroenterol* 2020;115:603-7.
73 Jacobs JP, Gupta A, Bhatt RR, et al, Cognitive behavioral therapy for irritable bowel syndrome induces bidirectional alterations in the brain-gut-microbiome axis associated with gastrointestinal symptom improvement. *Microbiome* 2021;9:236.
74 Keefer L, Ballou SK, Drossman DA, Ringstrom G, Elsenbruch S, Ljótsson B. A Rome working team report on brain-gut

behavior therapies for disorders of gut-brain interaction. *Gastroenterology* 2022;162:300-15.
75 Sugaya N, Shirotsuki K, Nakao M. Cognitive behavioral treatment for irritable bowel syndrome: a recent literature review. *Biopsychosoc Med* 2021;15:23.
76 Palsson OS. Hypnosis treatment of gastrointestinal disorders: a comprehensive review of the empirical evidence. *Am J Clin Hypn* 2015;58:134-58.
77 Moser G, Trägner S, Gajowniczek EE, 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.
78 Lindfors P, Unge P, Nyhlin H, et al, Long-term effects of hypnotherapy in patients with refractory irritable bowel syndrome. *Scand J Gastroenterol* 2012;47:414-20.
79 Gonsalkorale WM, Miller V, Afzal A, Whorwell PJ. Long term benefits of hypnotherapy for irritable bowel syndrome. *Gut* 2003;52:1623-9.
80 Burton Murray H, Ljótsson B. Burton Murray H, Ljótsson B. Future of brain–gut behavior therapies: Mediators and moderators. *Gastroenterol Clin North Am* 2022;51:723-39.
81 Banerjee A, Sarkhel S, Sarkar R, Dhali GK. Anxiety and depression in irritable bowel syndrome. *Indian J Psychol Med* 2017;39:741-5.
82 Moloney RD, Johnson AC, O'Mahony SM, Dinan TG, Greenwood-Van Meerveld B, Cryan JF. Stress and the microbiota-gut-brain axis in visceral pain: relevance to irritable bowel syndrome. *CNS Neurosci Ther* 2016;22:102-17.
83 Kinsinger SW. Cognitive-behavioral therapy for patients with irritable bowel syndrome: current insights. *Psychol Res Behav Manag* 2017;10:231-7.
84 Keefer L, Palsson OS, Pandolfino JE. Best practice update: incorporating psychogastroenterology into management of digestive disorders. *Gastroenterology* 2018;154:1249-57.
85 Thakur ER, Shapiro J, Chan J, et al, A systematic review of the effectiveness of psychological treatments for IBS in gastroenterology settings: promising but in need of further study. *Dig Dis Sci* 2018;63:2189-201.
86 Mirsharifa SM, Mirzaian B, Dousti Y. The efficacy of acceptance and commitment therapy (ACT) matrix on depression and psychological capital of the patients with irritable bowel syndrome. *Open Access Maced J Med Sci* 2019;7:421-7.
87 Sebastián Sánchez B, Gil Roales-Nieto J, Ferreira NB, Gil Luciano B, Sebastián Domingo JJ. New psychological therapies for irritable bowel syndrome: mindfulness, acceptance and commitment therapy (ACT). *Rev Esp Enferm Dig* 2017;109:648-57.
88 Black CJ, Thakur ER, Houghton LA, Quigley EMM, Moayyedi P, Ford AC. Efficacy of psychological therapies for irritable bowel syndrome: systematic review and network meta-analysis. *Gut* 2020;69:1441-51.
89 Liegl G, Plessen CY, Leitner A, Boeckle M, Pieh C. Guided self-help interventions for irritable bowel syndrome: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2015;27:1209-21.
90 Pajak R, Lackner J, Kamboj SK. A systematic review of minimal-contact psychological treatments for symptom management in irritable bowel syndrome. *J Psychosom Res* 2013;75:103-12.
91 Zernicke KA, Campbell TS, Blustein PK, et al, Mindfulness-based stress reduction for the treatment of irritable bowel syndrome symptoms: a randomized wait-list controlled trial. *Int J Behav Med* 2013;20:385-96.
92 Hyphantis T, Guthrie E, Tomenson B, Creed F. Psychodynamic interpersonal therapy and improvement in interpersonal difficulties in people with severe irritable bowel syndrome. *Pain* 2009;145:196-203.
93 Farnam A, Somi MH, Farhang S, Mahdavi N, Ali Besharat M. The therapeutic effect of adding emotional awareness training to standard medical treatment for irritable bowel syndrome: a randomized clinical trial. *J Psychiatr Pract* 2014;20:3-11.
94 Laird KT, Stanton AL. Written expressive disclosure in adults with irritable bowel syndrome: A randomized controlled trial. *Complement Ther Clin Pract* 2021;43:101374.
95 Thakur ER, Holmes HJ, Lockhart NA, et al, Emotional awareness and expression training improves irritable bowel syndrome: A randomized controlled trial. *Neurogastroenterol Motil* 2017;29:29.
96 Mohsenabadi H, Zanjani Z, Shabani MJ, Arj A. A randomized clinical trial of the Unified Protocol for Transdiagnostic treatment of emotional and gastrointestinal symptoms in patients with irritable bowel syndrome: evaluating efficacy and mechanism of change. *J Psychosom Res* 2018;113:8-15.
97 Kikuchi S, Oe Y, Ito Y, et al, Group cognitive-behavioral therapy with interoceptive exposure for drug-refractory irritable bowel syndrome: a randomized controlled trial. *Am J Gastroenterol* 2022;117:668-77.
98 Lövdahl J, Törnblom H, Ringström G, Palsson OS, Simrén M. Randomised clinical trial: individual versus group hypnotherapy for irritable bowel syndrome. *Aliment Pharmacol Ther* 2022;55:1501-11.
99 Owusu JT, Sibelli A, Moss-Morris R, van Tilburg MAL, Levy RL, Oser M. A pilot feasibility study of an unguided, internet-delivered cognitive behavioral therapy program for irritable bowel syndrome. *Neurogastroenterol Motil* 2021;33:e14108.
100 Everitt HA, Landau S, O'Reilly G, et al, ACTIB trial group. 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.
101 Everitt HA, Landau S, O'Reilly G, 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.
102 Hunt M, Miguez S, Dukas B, Onwude O, White S. Efficacy of Zemedy, a mobile digital therapeutic for the self-management of irritable bowel syndrome: crossover randomized controlled trial. *JMIR Mhealth Uhealth* 2021;9:e26152.
103 Peters SL, Gibson PR, Halmos EP. Smartphone app-delivered gut-directed hypnotherapy improves symptoms of self-reported irritable bowel syndrome: a retrospective evaluation. *Neurogastroenterol Motil* 2023;35:e14533.
104 Berry SK, Berry R, Recker D, Botbyl J, Pun L, Chey WD. A randomized parallel-group study of digital ut-directed hypnotherapy vs muscle relaxation for irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2023;21:3152-3159.e2.
105 Hasan SS, Pearson JS, Morris J, Whorwell PJ. SKYPE hypnotherapy for irritable bowel syndrome: effectiveness and comparison with face-to-face treatment. *Int J Clin Exp Hypn* 2019;67:69-80.
106 Ingrosso MR, Ianiro G, Nee J, et al, Systematic review and meta-analysis: efficacy of peppermint oil in irritable bowel syndrome. *Aliment Pharmacol Ther* 2022;56:932-41.
107 Maselli DB, Camilleri M. Pharmacology, clinical effects, and therapeutic potential of cannabinoids for gastrointestinal and liver diseases. *Clin Gastroenterol Hepatol* 2021;19:1748-1758.e2.
108 Sharkey KA, Wiley JW. The role of the endocannabinoid system in the brain-gut axis. *Gastroenterology* 2016;151:252-66.
109 van Orten-Luiten AB, de Roos NM, Majait S, Witteman BJM, Witkamp RF. Effects of cannabidiol chewing gum on perceived pain and well-being of irritable bowel syndrome patients: a placebo-controlled crossover exploratory intervention study with symptom-driven dosing. *Cannabis Cannabinoid Res* 2022;7:436-44.
110 Patel RS, Goyal H, Satodiya R, Tankersley WE. Relationship of cannabis use disorder and irritable bowel syndrome (IBS): an analysis of 6.8 million hospitalizations in the United States. *Subst Use Misuse* 2020;55:281-90.
111 Esfandyari T, Camilleri M, Busciglio I, Burton D, Baxter K, Zinsmeister AR. Effects of a cannabinoid receptor agonist on colonic motor and sensory functions in humans: a randomized, placebo-controlled study. *Am J Physiol Gastrointest Liver Physiol* 2007;293:G137-45.
112 Klooker, TK, Leliefeld KEM, Van Den Wijngaard RM, et al, The cannabinoid receptor agonist delta-9-tetrahydrocannabinol does not affect visceral sensitivity to rectal distension in healthy volunteers and IBS patients. *Neurogastroenterol Motil* 2011;23:30-5, e2.
113 Wong, BS, Camilleri M, Busciglio I, et al, Pharmacogenetic trial of a cannabinoid agonist shows reduced fasting colonic motility in patients with nonconstipated irritable bowel syndrome. *Gastroenterology* 2011;141:1638-47.
114 Wong BS, Camilleri M, Eckert D, et al, Randomized pharmacodynamic and pharmacogenetic trial of dronabinol effects on colon transit in irritable bowel syndrome-diarrhea. *Neurogastroenterol Motil* 2012;24:358-e169.
115 Chang L, Cash BD, Lembo A, et al, Efficacy and safety of olorinab, a full agonist of the cannabinoid receptor 2, for the treatment of abdominal pain in patients with irritable bowel syndrome: Results from a phase 2b randomized placebo-controlled trial (CAPTIVATE). *Neurogastroenterol Motil* 2023;35:e14539.
116 Zhu JJ, Liu S, Su XL, et al, Efficacy of Chinese herbal medicine for diarrhea-predominant irritable bowel syndrome: a meta-analysis of randomized, double-blind, placebo-controlled trials. *Evid Based Complement Alternat Med* 2016;2016:4071260.
117 Fan H, Zheng L, Lai Y, et al, China Irritable Bowel Syndrome Consortium. Tongxie formula reduces symptoms of irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2017;15:1724-32.
118 Chen M, Qin D, Huang SL, Tang TC, Zheng H. Chinese herbal medicine versus antispasmodics in the treatment of irritable bowel syndrome: A network meta-analysis. *Neurogastroenterol Motil* 2021;33:e14107.
119 Lauche R, Kumar S, Hallmann J, et al, Efficacy and safety of Ayurvedic herbs in diarrhoea-predominant irritable bowel syndrome: A randomised controlled crossover trial. *Complement Ther Med* 2016;26:171-7.
120 Oka T, Okumi H, Nishida S, et al, JOPM-EBM Working Team. Effects of Kampo on functional gastrointestinal disorders. *Biopsychosoc Med* 2014;8:5.

121 Portincasa P, Bonfrate L, Scribano ML, et al, Curcumin and fennel essential oil improve symptoms and quality of life in patients with irritable bowel syndrome. *J Gastrointestin Liver Dis* 2016;25:151-7.
122 Quezada SM, Cross RK. Cannabis and turmeric as complementary treatments for IBD and other digestive diseases. *Curr Gastroenterol Rep* 2019;21:2.
123 Lauche R, Janzen A, Lüdtke R, Cramer H, Dobos G, Langhorst J. Efficacy of caraway oil poultices in treating irritable bowel syndrome—a randomized controlled cross-over trial. *Digestion* 2015;92:22-31.
124 Chen KH, Zeng BY, Zeng BS, et al, The efficacy of exogenous melatonin supplement in ameliorating irritable bowel syndrome severity: A meta-analysis of randomized controlled trials. *J Formos Med Assoc* 2023;122:276-85.
125 Størsrud S, Pontén I, Simrén M. A pilot study of the effect of Aloe barbadensis mill extract (AVH200®) in patients with irritable bowel syndrome: a randomized, double-blind, placebo-controlled study. *J Gastrointestin Liver Dis* 2015;24:275-80.
126 van Tilburg MA, Palsson OS, Ringel Y, Whitehead WE. Is ginger effective for the treatment of irritable bowel syndrome? A double blind randomized controlled pilot trial. *Complement Ther Med* 2014;22:17-20.
127 Chen C, Tao C, Liu Z, et al, A randomized clinical trial of berberine hydrochloride in patients with diarrhea-predominant irritable bowel syndrome. *Phytother Res* 2015;29:1822-7.
128 Allescher HD, Abdel-Aziz H. Mechanism of action of STW 5 in functional dyspepsia and IBS: the origin of multi-target. *Dig Dis* 2017;35(Suppl 1):18-24.
129 Lapina TL, Trukhmanov AS. Herbal preparation STW 5 for functional gastrointestinal disorders: clinical experience in everyday practice. *Dig Dis* 2017;35(Suppl 1):30-5.
130 Britannica T. *Acupuncture*, in *Encyclopedia Britannica*, Encyclopaedia
131 Ma XP, Hong J, An CP, et al, Acupuncture-moxibustion in treating irritable bowel syndrome: how does it work?*World J Gastroenterol* 2014;20:6044-54.
132 Liang C, Wang KY, Gong MR, Li Q, Yu Z, Xu B. Electro-acupuncture at ST37 and ST25 induce different effects on colonic motility via the enteric nervous system by affecting excitatory and inhibitory neurons. *Neurogastroenterol Motil* 2018;30:e13318.
133 Zhao JM, Lu JH, Yin XJ, et al, Comparison of electroacupuncture and moxibustion on brain-gut function in patients with diarrhea-predominant irritable bowel syndrome: A randomized controlled trial. *Chin J Integr Med* 2015;21:855-65.
134 Zhenzhong L, Xiaojun Y, Weijun T, et al, Comparative effect of electroacupuncture and moxibustion on the expression of substance P and vasoactive intestinal peptide in patients with irritable bowel syndrome. *J Tradit Chin Med* 2015;35:402-10.
135 Zhao JM, Lu JH, Yin XJ, et al, Comparison of electroacupuncture and mild-warm moxibustion on brain-gut function in patients with constipation-predominant irritable bowel syndrome: a randomized controlled trial. *Chin J Integr Med* 2018;24:328-35.
136 Lim B, Manheimer E, Lao L, et al, Acupuncture for treatment of irritable bowel syndrome. *Cochrane Database Syst Rev* 2006;(4):CD005111.
137 Chao GQ, Zhang S. Effectiveness of acupuncture to treat irritable bowel syndrome: a meta-analysis. *World J Gastroenterol* 2014;20:1871-7.
138 Zhu L, Ma Y, Ye S, et al, Acupuncture for diarrhoea-predominant irritable bowel syndrome: a network meta-analysis. *Evid Based Complement Alternat Med* 2018:2890465.
139 Wu IXY, Wong CHL, Ho RST, et al, Acupuncture and related therapies for treating irritable bowel syndrome: overview of systematic reviews and network meta-analysis. *Therap Adv Gastroenterol* 2019;12:1756284818820438.
140 Zheng H, Chen R, Zhao X, et al, Comparison between the effects of acupuncture relative to other controls on irritable bowel syndrome: a meta-analysis. *Pain Res Manag* 2019;2019:2871505.
141 MacPherson H, Tilbrook H, Agbedjro D, Buckley H, Hewitt C, Frost C. Acupuncture for irritable bowel syndrome: 2-year follow-up of a randomised controlled trial. *Acupunct Med* 2017;35:17-23.
142 Huang J, Lu M, Zheng Y, et al, Quality of evidence supporting the role of acupuncture for the treatment of irritable bowel syndrome. *Pain Res Manag* 2021;2021:2752246.
143 Lowe C, Aiken A, Day AG, Depew W, Vanner SJ. Sham acupuncture is as efficacious as true acupuncture for the treatment of IBS: A randomized placebo controlled trial. *Neurogastroenterol Motil* 2017;29.
144 Su X-T, Wang LQ, Zhang N, et al, Standardizing and optimizing acupuncture treatment for irritable bowel syndrome: A Delphi expert consensus study. *Integr Med Res* 2021;10:100728.
145 Wong WK, Chien WT, Lee WM. Self-administered acupressure for treating adult psychiatric patients with constipation: a randomized controlled trial. *Chin Med* 2015;10:32.
146 Abbasi P, Mojalli M, Kianmehr M, Zamani S. Effect of acupressure on constipation in patients undergoing hemodialysis: A randomized double-blind controlled clinical trial. *Avicenna J Phytomed* 2019;9:84-91.
147 Xu XH, Zhang MM, Wu X, et al, Efficacy of electro-acupuncture in treatment of functional constipation: a randomized controlled trial. *Curr Med Sci* 2020;40:363-71.
148 Chen CY, Ke MD, Kuo CD, Huang CH, Hsueh YH, Chen JR. The influence of electro-acupuncture stimulation to female constipation patients. *Am J Chin Med* 2013;41:301-13.
149 Health, N.C.f.C.a.I., *The Science of Mind-Body Therapies*.
150 Johannesson E, Ringström 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.
151 Hajizadeh Maleki B, Tartibian B, Mooren FC, et al, Low-to-moderate intensity aerobic exercise training modulates irritable bowel syndrome through antioxidative and inflammatory mechanisms in women: Results of a randomized controlled trial. *Cytokine* 2018;102:18-25.
152 Zhao S-R, Ni XM, Zhang XA, Tian H. Effect of cognitive behavior therapy combined with exercise intervention on the cognitive bias and coping styles of diarrhea-predominant irritable bowel syndrome patients. *World J Clin Cases* 2019;7:3446-62.
153 Zhou C, Zhao E, Li Y, Jia Y, Li F. Exercise therapy of patients with irritable bowel syndrome: A systematic review of randomized controlled trials. *Neurogastroenterol Motil* 2019;31:e13461.
154 Nunan D, Cai T, Gardener AD, et al, Physical activity for treatment of irritable bowel syndrome. *Cochrane Database Syst Rev* 2022;6:CD011497.
155 Streeter CC, Gerbarg PL, Saper RB, Ciraulo DA, Brown RP. Effects of yoga on the autonomic nervous system, gamma-aminobutyric-acid, and allostasis in epilepsy, depression, and post-traumatic stress disorder. *Med Hypotheses* 2012;78:571-9.
156 Arora S, Bhattacharjee J. Modulation of immune responses in stress by Yoga. *Int J Yoga* 2008;1:45-55.
157 Schumann D, Anheyer D, Lauche R, Dobos G, Langhorst J, Cramer H. Effect of yoga in the therapy of irritable bowel syndrome: a systematic review. *Clin Gastroenterol Hepatol* 2016;14:1720-31.
158 D'Silva A, Marshall DA, Vallance JK, et al, Meditation and yoga for irritable bowel syndrome: a randomized clinical trial. *Am J Gastroenterol* 2023;118:329-37.
159 Staller K, Paz M, Rones R, et al, Virtual Tai Chi program for patients with irritable bowel syndrome with constipation: Proof-of-concept feasibility trial. *Neurogastroenterol Motil* 2022;34:e14429.
160 Müller A, Franke H, Resch KL, Fryer G. Effectiveness of osteopathic manipulative therapy for managing symptoms of irritable bowel syndrome: a systematic review. *J Am Osteopath Assoc* 2014;114:470-9.
161 Grosjean D, Benini P, Carayon P. Managing irritable bowel syndrome: The impact of micro-physiotherapy. *J Complement Integr Med* 2017;14:14.
162 Schulze NB, Salemi MM, de Alencar GG, Moreira MC, de Siqueira GR. Efficacy of manual therapy on pain, impact of disease, and quality of life in the treatment of fibromyalgia: a systematic review. *Pain Physician* 2020;23:461-76.
163 Goldenberg JZ, Brignall M, Hamilton M, et al, Biofeedback for treatment of irritable bowel syndrome. *Cochrane Database Syst Rev* 2019;2019:CD012530.
164 Howell CA, Mikhalovsky SV, Markaryan EN, Khovanov AV. Investigation of the adsorption capacity of the enterosorbent Enterosgel for a range of bacterial toxins, bile acids and pharmaceutical drugs. *Sci Rep* 2019;9:5629.
165 Howell CA, Markaryan E, Allgar V, 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.
166 Howell CA, Kemppinen A, Allgar V, 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.
167 Jiang Y, Soffer E. Electroceuticals for neurogastroenterology and motility disorders. *Curr Gastroenterol Rep* 2023;03.
168 Bonaz B. Anti-inflammatory effects of vagal nerve stimulation with a special attention to intestinal barrier dysfunction. *Neurogastroenterol Motil* 2022;34:e14456.
169 Shi X, Hu Y, Zhang B, Li W, Chen JD, Liu F. Ameliorating effects and mechanisms of transcutaneous auricular vagal nerve stimulation on abdominal pain and constipation. *JCI Insight* 2021;6:22.
170 Kovacic K, Hainsworth K, Sood M, et al, Neurostimulation for abdominal pain-related functional gastrointestinal disorders in adolescents: a randomised, double-blind, sham-controlled trial. *Lancet Gastroenterol Hepatol* 2017;2:727-37.
171 Rao SSC, Quigley EMM, Chey WD, Sharma A, Lembo AJ. Randomized placebo-controlled phase 3 trial of vibrating capsule for chronic constipation. *Gastroenterology* 2023;164:1202-1210.e6.
172 Zhu JH, Qian YY, Pan J, et al, Efficacy and safety of vibrating capsule for functional constipation (VICONS): A randomised,

double-blind, placebo-controlled, multicenter trial. *EClinicalMedicine* 2022;47:101407.
173 Nelson AD, Camilleri M, Acosta A, et al, A single-center, prospective, double-blind, sham-controlled, randomized study of the effect of a vibrating capsule on colonic transit in patients with chronic constipation. *Neurogastroenterol Motil* 2017;29:29.
174 Lacy BE, Cangemi DJ, Spiegel BR. Virtual reality: a new treatment paradigm for disorders of gut-brain interaction?*Gastroenterol Hepatol (N Y)* 2023;19:86-94.
175 Spiegel BMR, Liran O, Gale R, et al, Qualitative validation of a novel VR program for irritable bowel syndrome: A VR1 study. *Am J Gastroenterol* 2022;117:495-500.