gastroenterology insights

MDPI

Review

Irritable Bowel Syndrome: Current Landscape of Diagnostic Guidelines and Therapeutic Strategies

Dareen S. Chuy [1], Ryan S. Wi [1] and Micheal Tadros [2,*]

[1] Albany Medical College, Albany, NY 12208, USA; chuyd@amc.edu (D.S.C.); wir1@amc.edu (R.S.W.)
[2] Department of Gastroenterology, Albany Medical Center, Albany, NY 12208, USA
* Correspondence: tadrosm1@amc.edu

Abstract: Irritable bowel syndrome (IBS) is a disorder of the gut–brain axis with pronounced adverse effects on physical health, psychological health, and overall quality of life. Diagnostic strategies can vary, highlighting a need to synthesize best-practice guidelines. Particularly, the American College of Gastroenterology and the British Society of Gastroenterology both support a positive diagnostic strategy; evaluation with C-reactive protein, fecal calprotectin, and fecal lactoferrin; and evaluation with celiac disease serology. Both guidelines do not support routine colonoscopy, and both differ in recommendations for anorectal physiology testing. Given there is currently no curative treatment available, IBS management focuses on symptomatic relief, and challenges exist in achieving and maintaining this relief. Many treatments, both pharmacologic and nonpharmacologic, exist to alleviate the uncomfortable, painful symptoms of the disorder; however, stratifying the quality of evidence behind each option is critical for application to clinical management and for tailoring this management to each patient. Lifestyle adjustments, especially in relation to diet, can be effective first-line therapies and supplements to pharmacologic therapy. Pharmacologic treatment is broadly categorized in accordance with the subtypes of IBS, with indications for different populations and mechanisms that work to target components of IBS pathophysiology. The aim of this article is to comprehensively compare updated diagnostic guidelines, review standard treatments, and outline recent pharmacologic advancements.

Keywords: irritable bowel syndrome; diagnostic guidelines; pharmacology

Citation: Chuy, D.S.; Wi, R.S.; Tadros, M. Irritable Bowel Syndrome: Current Landscape of Diagnostic Guidelines and Therapeutic Strategies. *Gastroenterol. Insights* **2024**, *15*, 786–809. https://doi.org/10.3390/gastroent15030056

Academic Editor: Ludovico Abenavoli

Received: 21 June 2024
Revised: 17 August 2024
Accepted: 6 September 2024
Published: 9 September 2024

1. Introduction

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder with a significant global burden. The disorder has a cited prevalence of 11% worldwide; however, prevalence can vary substantially between countries and is dependent on the diagnostic or definitional criteria used, study methodology, and individual sociocultural factors [1]. Nevertheless, IBS is the most commonly diagnosed gastrointestinal disorder [2] and has critical effects on not only health but also importantly quality of life (QoL). QoL is negatively affected by IBS, especially in those who have predominant diarrhea. Patients may avoid certain social situations secondary to incontinence fears, and there are concomitant reports of feelings of decreased freedom [1]. Stigmatization can foster isolation, and interference with work (absenteeism, loss of socialization opportunities, loss of earnings) can further contribute to poor QoL [1].

IBS involves changes in stooling habits that cause symptoms of abdominal pain or discomfort; however, there is an absence of an underlying organic abnormality or disease process. There are four overarching subtypes of IBS: diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), mixed (IBS-M), and unclassified (IBS-U) [3]. Diagnosis of IBS is often guided by the Rome criteria (most recently Rome IV), such that abdominal pain has occurred at least one day per week in the past three months, and there is the presence of at least two of the following criteria with regard to the pain: related to defecation, associated with change in stool frequency, associated with change in stool appearance [3].

The pathophysiology of IBS is complex, encompassing, but not limited to, motility abnormalities, visceral pain hypersensitivity, inflammation, brain–gut interactions, and

psychosocial distress. IBS symptomatology may result from an interaction between low thresholds for stimuli and motility abnormalities. Changes in motility in IBS can involve increased gut responsiveness (e.g., increased phasic contractions) to stimuli such as meals, cholecystokinin, and distention [4]. Greater gut motility responses to stimuli may also work in parallel with greater patient perception of visceral pain in the development of symptomatology [5]. This is supported by studies finding that with gut balloon distention, those with IBS have reported pain hypersensitivity and increased activation of brain regions involved in emotional arousal and pain modulation [6]. There is also the implication of a potential gut immune role in IBS. Studies have found upregulated immune cellularity (e.g., mast cells, lymphocytes) in the colons of patients with IBS [4]. Additionally, post-infectious IBS, in which there is a reported temporal association between IBS symptom development and gastroenteritis, supports the possible involvement of inflammation secondary to immune processes [7]. Lastly, psychosocial components are essential. Psychosocial distress and the frequent psychiatric comorbidities in IBS contribute to disorder development, symptom exacerbation, and treatment outcomes [7,8].

Novel theories regarding the pathophysiology of IBS continue to emerge as well. Recently, there has been increasing evidence for the role of stem cells in gastrointestinal disorders, particularly in inflammatory bowel disease (IBD). Stem cells have the ability to differentiate into various types of progeny and can self-renew [9]. In IBD, dysfunctional or non-functional intestinal resident stem cells can disrupt intestinal homeostasis and contribute to the chronic inflammation observed in the disease [9]. Studies, both in rodent models and in clinical trials, implementing mesenchymal stem cell therapies have shown success in exhibiting anti-inflammatory effects and in treating refractory IBD [10,11]. Less is known, however, on how stem cells may be implicated in IBS. A hypothesis by El-Salhy suggests an interconnection between genetic and environmental factors influencing stem cells in the gut [12]. It has been shown that there is a lower density of enteroendocrine cells in those with IBS, which may be attributed to abnormal stem cells; stem cell dysfunction and reduced differentiation may in turn be secondary to gene mutations, specifically NEUROG3 mutations. A genetic hypothesis may synergistically work with an environmental hypothesis, in which factors such as diet, stress, and the gut microbiome can impact stem cell function [12]. In all, more research is certainly needed to explore these hypotheses and better assess the impact of stem cells on clinical management.

Given the complexity of the pathophysiology underlying IBS, treatment approaches aim to target the various processes that have been implicated. Treatment can be challenging due to the heterogeneous phenotypes of the disorder, and symptoms can often recur despite treatment [13–15]. As the list of both nonpharmacologic and pharmacologic therapies grows, this clinical review aims to cover established, available treatments and recent advancements. This review also aims to provide an overview and comparison of diagnostic recommendations by national guidelines.

2. IBS Diagnostic Approach: American College of Gastroenterology (ACG) and British Society of Gastroenterology (BSG) Comparison

2.1. Positive Diagnostic Strategy

Both the ACG and BSG endorse a positive diagnostic strategy, rather than a strategy of exclusion. A positive strategy centers on making an IBS diagnosis based on patient symptoms via detailed clinical history and strays from a reliance on more invasive diagnostic testing [16,17]. The Rome criteria is one such symptom-based diagnostic criteria that can be referenced in the IBS workup. The BSG additionally points to the National Institute for Health and Care Excellence (NICE) guideline for primary care IBS evaluation, which is less restrictive than the Rome criteria. NICE guidelines indicate consideration for IBS workup if there is any abdominal pain/discomfort, bloating, and/or alteration in bowel habits for at least six months [17].

Studies cited by the ACG have supported that further diagnostic testing associated with a strategy of exclusion is low yield [16]. A study by Begtrup, et al. looked at patients

in primary care with clinical suspicion of IBS and no alarm signs who also met Rome III criteria, randomizing the population to a positive strategy versus a strategy of exclusion. A positive strategy only included complete blood count and C-reactive protein (CRP), while a strategy of exclusion additionally included sigmoidoscopy with biopsy and stool parasite culture. A positive strategy was found to be noninferior to a strategy of exclusion and was associated with fewer costs [18]. Sayuk, et al. also found that those who were diagnosed with IBS-D with a positive strategy were more likely to already be connected with evidence-based treatment than those who were formally undiagnosed but still affected by IBS-D symptoms [19]. Therefore, making a positive, symptom-based diagnosis, especially at the primary care level, importantly shortens the time to therapy initiation.

2.2. CRP, Fecal Calprotectin, and Fecal Lactoferrin

IBS evaluation with fecal calprotectin, fecal lactoferrin, and CRP is strongly recommended by the ACG and BSG. The ACG recommends assessing either fecal calprotectin or fecal lactoferrin and CRP in patients with suspected IBS with diarrhea and no alarm features to rule out IBD. Fecal calprotectin along with CRP evaluation is considered by the ACG to potentially be superior to fecal lactoferrin [16]. The BSG recommends assessing CRP in all patients who present to primary care for the first time with IBS symptoms; fecal calprotectin is recommended to rule out IBD in patients less than 45 years of age with IBS symptoms including diarrhea [17].

A meta-analysis performed by Menees, et al. found that CRP $\leq$ 0.5 and fecal calprotectin $\leq$ 40 μg/g both can exclude a diagnosis of IBD in patients with IBS symptoms, whereas erythrocyte sedimentation rate and fecal lactoferrin had low utility based on this analysis [20]. Another meta-analysis has shown fecal calprotectin sensitivity and specificity for IBD to be 93% (CI = 85–97%) and 96% (CI = 79–99%), respectively [21]. A meta-analysis has also shown fecal lactoferrin sensitivity and specificity for identifying IBD versus IBS to be 78% (CI =75–82%) and 94% (CI 91–96%), respectively [22]. In all, testing for CRP, fecal calprotectin, and fecal lactoferrin is noninvasive and safe and has evidence-based utility in the evaluation of IBD versus IBS [16]. Of note, the BSG points out that the use of these markers may improve risk stratification and refine secondary care referrals [17].

2.3. Celiac Disease Serology

The ACG and BSG support celiac disease serology testing in those with IBS symptoms. Specifically, the ACG recommends serology screening (IgA tissue transglutaminase and quantitative IgA level) in those with IBS-D symptoms, in accordance with ACG celiac disease guidelines [16]. The BSG recommends testing in all patients presenting for the first time to primary care with IBS symptoms [17].

Abnormal celiac disease serology has been found to be three times greater in those with IBS symptoms than those with no IBS symptoms [23]. This metanalysis of international studies by Irvine, et al. supported a significantly increased likelihood of positive IgA, anti-endomysial antibodies, and/or tissue transglutaminase antibodies and an increased likelihood of biopsy-proven celiac disease in patients with IBS symptoms. The highest prevalence of celiac disease was reported in those with IBS-D symptoms [23]. Notably, odds ratios were not increased in the included North American studies [23]; a study by Cash, et al. similarly found no significant differences in celiac disease prevalence in those with symptoms of non-constipated IBS versus control in a U.S. population [24]. While the ACG acknowledges the limitations of these results, especially in North America, they still recommend serology screening [16]. Given that the abdominal symptoms in celiac disease and IBS can often be mistaken for one another and given the consequences of a missed celiac disease diagnosis, early screening during evaluation can be highly beneficial and cost-effective [16].

2.4. Colonoscopy

Overall, the ACG and BSG do not support routine colonoscopy for IBS evaluation (independent of colon cancer screening), despite it being a frequently used test. The

evidence for colonoscopy in IBS is graded as poor, and it is considered very low yield; there is also low evidence for reassurance or improved QoL in those with a negative colonoscopy [17,25,26].

Generally, certain alarm features (e.g., weight loss, hematochezia, melena, familial colon cancer history) may prompt providers to seek colonoscopy for further workup; however, it is important to note that investigation of these symptoms in those with IBS has low predictive value [16,25,27].

The BSG endorses consideration of colonoscopy in evaluations to exclude microscopic colitis in patients with diarrhea and other characteristics: female; age ≥ 50; autoimmune disease; severe nocturnal, watery diarrhea; weight loss; use of non-steroidal anti-inflammatory drugs (NSAIDs), proton-pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs), and statins [17]. On the other hand, while the ACG acknowledges that colonoscopy in female patients over the age of 60 with suspected IBS-D to rule out microscopic colitis is a special case, they assert that the evidence to justify colonoscopy is still limited [16].

2.5. Anorectal Physiology Testing

The recommendation of anorectal physiology testing, such as anorectal manometry (ARM) and balloon expulsion test (BET), is weak by the BSG and suggested by the ACG. It is suggested by the ACG to perform testing in those with symptoms more in alignment with underlying pelvic floor dysfunction and/or the presence of constipation that is refractory to first-line, standard treatment [16]. Anorectal physiology testing is weakly recommended by the BSG for those with symptoms suggestive of fecal incontinence or a defecatory disorder (e.g., straining, sensation of incomplete defecation) and if it is determined that pelvic floor biofeedback therapy would be beneficial for the patient [17].

Anorectal dysfunction has been found to occur in all IBS subtypes [16]. The ACG particularly highlights the potential utility of physiology testing in distinguishing IBS from dyssynergic defecation (DD), which requires physiologic testing for proper diagnosis, as the two can share mutual characteristics in symptomatology [16]. A study by Mulak, et al. looked at patients meeting Rome III criteria undergoing ARM, finding that pelvic floor dyssynergia was more frequent in all IBS subgroups compared to control ($p < 0.01$) [28]. Patients with non-diarrhea-predominant IBS have also been found to have pelvic floor dyssynergia similar to functional constipation and an even greater prevalence of abnormal BET results [29].

Since abdominal pain and defecation patterns in DD positively respond to biofeedback therapy [16,30,31], differentiating between IBS and DD via physiology testing warrants consideration in patients who have been refractory to conventional treatment approaches. In doing so, subsequent targeting of pelvic floor dysfunction may improve outcomes in this subset of patients.

3. IBS Management

Management of IBS symptoms and maintenance of relief long-term can be challenging. Prior to pharmacologic management, lifestyle modifications (e.g., exercise, stress reduction, sleep hygiene) and particularly diet should be addressed. From there, pharmacologic treatment options can be trialed based upon the symptom-predominant subtype and in accordance with best-practice guidelines (Figure 1).

3.1. Dietary Modification

Diet plays a significant role in IBS symptoms and treatment. Hypersensitivity or intolerance to any foods may cause low-grade inflammation and visceral hypersensitivity, both of which have been implicated in the underlying pathophysiology of IBS [7,32]. Additionally, nutrients in general can influence gut microbiota, motility, and sensitivity [7,32]. Therefore, incorporating dietary counseling and changes are notable components of IBS management. Best-practice guidelines suggest that the best candidates for restrictive dietary interventions are those with knowledge of food-related gastrointestinal symptoms and

motivation to implement changes. Poor candidates include those who have eating-related psychiatric conditions, who are food-insecure, and who may be at risk for malnutrition [25].

3.1.1. Low-FODMAP Diet

The low-fermentable oligosaccharide, disaccharide, monosaccharide, and polyol (low-FODMAP) diet is the diet with the most evidence-based support in IBS patients [25]. FODMAPs are short-chain carbohydrates with adverse implications for gut homeostasis. They have poor intestinal absorption and undergo high fermentation, producing methane, hydrogen, and carbon dioxide gases in the guts of those with IBS [14,33]. The diet aims to limit high-FODMAP foods—foods high in fructose (e.g., fruits, honey sweeteners), lactose (animal-based dairy products such as yogurt, milk, ice cream), fructans and galactooligosaccharides (e.g., brussels sprouts, onions, legumes, beans), and polyols (e.g., pears, apples, cauliflower, artificial sweeteners) [32–34]. Studies have supported the efficacy of the low-FODMAP diet in the management of IBS by reducing symptoms, especially abdominal pain and bloating, and improving reported QoL [25,35].

There are three phases to the diet: restriction, reintroduction, and personalization. Restriction is conducted over four to six weeks with the goal of knowing whether symptoms are associated with FODMAPs. FODMAPs are then reintroduced over time in the second phase to identify specific food or ingredient triggers. Diet is then personalized in the third phase depending on the results of reintroduction; the personalized diet should ideally center on non-triggering foods while limiting and/or substituting triggering foods [14,25]. While there may be some concern over potential nutritional inadequacies due to the restrictive nature of the diet, studies rather overall support nutritional adequacy [36]. Fiber, fat, and protein in IBS patients following the low-FODMAP diet have been found to be comparable to controls [37]. While there is a study by Staudacher and colleagues reporting a decline in calcium with this diet, inadequate substitution with lactose-free, high-calcium products may be an attributable cause [37,38].

3.1.2. Soluble Fibers

Broadly, fibers are carbohydrates that are not digested or absorbed in the small intestines and can be characterized by solubility, viscosity, and fermentability. Soluble fibers specifically have been recommended for the treatment of global IBS symptoms and can be found in psyllium, barley, oats, and beans [16]. Soluble fibers can increase stool bulk, decrease gut transit times, and decrease colonic pressures by fermenting into gas and short-chain fatty acid byproducts [39,40]. It is important that the chosen soluble fiber has only moderate fermentation, as fermentation may produce gases that contribute to abdominal pain or discomfort [16]. Oligosaccharides are short-chain, soluble, highly fermented fibers that promote flatulence, bloating, and abdominal pain in IBS. By contrast, psyllium is a soluble, viscous (gel-forming), minimally fermented fiber that helps improve stool consistency and has low gas production [39] (Table 1).

Table 1. Summary of Types of Soluble Fibers in the Management of IBS.

Soluble Fiber	Mechanism of Action	Origin	Common Brands
Psyllium	Stool bulking agent that draws water into the gut lumen	Plantago Ovata psyllium husk	Metamucil
Methylcellulose	Stool bulking agent that draws water into the gut lumen	Processed plant cellulose	Citrucel
Polycarbophil	Stool bulking agent that draws water into the gut lumen	Synthetic polymer of polyacrylic acid cross-linked with divinyl glycol	FiberCon

A systemic review and meta-analysis by Moayyedi, et al. of 14 randomized controlled trials supports the statistically significant efficacy of soluble fibers versus placebo (RR of IBS not improving = 0.86; 95% CI 0.80–0.94). Bran as an insoluble fiber was studied in six of the

trials and had no significant effects on IBS symptoms (RR of IBS not improving = 0.90; 95% CI 0.79–1.03; $p = 0.14$). Ispaghula husk (psyllium) was investigated as a soluble fiber in seven of the trials and led to significant improvement in symptoms (RR of IBS not improving = 0.83; 95% CI 0.73–0.94; $p = 0.005$). Combined analysis of adverse events in the six trials that included them showed no significant differences in general fiber use versus placebo; analysis of studies only using ispaghula similarly showed no significant differences [41].

3.2. Psychotherapy

The pathophysiology of IBS includes a complex relationship between biological, psychological, and social factors [42]. Addressing treatment at the level of the gut–brain axis using psychotherapies has shown to be an effective way to improve IBS refractory to conventional standards of care and pharmacotherapy. These treatments include cognitive behavioral therapy (CBT) and hypnotherapy.

CBT addresses emotional responses to how patients interpret and regulate input from the gut [16]. Many clinical trials support the utility of CBT for refractory IBS. One clinical trial conducted by Lackner, et al. investigated the use of CBT for IBS using three treatment arms: standard CBT (10 weeks of 60-minute in-person sessions), minimal contact CBT (four clinic visits over a 10-week period with emphasis on home study materials), and an education arm (centered around education and support) [43]. Using the Clinical Global Improvement Scale, patients receiving minimal contact CBT had significantly improved symptoms after 10 weeks ($p < 0.05$). Additionally, patients with improved symptoms in both CBT groups showed treatment response at every follow-up assessment in the 10-week period when compared to the education group ($p < 0.05$) [43]. Everitt, et al. conducted a trial looking at CBT treatment in adults with refractory IBS by comparing three treatment arms: telephone-based CBT, web-based CBT, and usual care [44]. Results showed that at a 24-month follow-up, a clinically significant change in IBS Symptom Severity Score (IBS-SSS) was found in 84 (71%) of 119 participants in the telephone-CBT group, in 62 (63%) of 99 in the web-CBT group, and in 48 (46%) of 105 in the usual care group [44]. Finally, a recent trial by Jacobs, et al. showed evidence of measurable changes in gut–brain behavior after CBT, including changes in gut microbiota and functional structural brain connectivity suggesting positive response and clinical improvement [45]. These trials support CBT as a viable treatment option for patients with refractory IBS.

In addition to CBT, hypnotherapy offers another psychotherapeutic option for refractory IBS. Interest in hypnotherapy for IBS began as early as 1984 in a 30-patient trial conducted by Whorwell, et al. that showed dramatic symptom improvement in patients receiving hypnotherapy versus placebo [46]. Later, Flik, et al. further investigated hypnotherapy for IBS in a trial comparing individual to group therapy. Patients were randomized to individual or group hypnotherapy versus group supportive therapy (control group) with the primary outcome defined as patients who reported adequate relief when asked once weekly for four consecutive weeks. In the results, individual and group hypnotherapy was more effective than the control group at three months (OR = 2.9; 95% CI 1.2–7.4; $p = 0.0240$) and 12 months (OR = 2.8; 95% CI 1.2–6.7; $p = 0.0185$) [47]. Lövdahl, et al. further validated these results in a similar clinical trial; improvement in the severity of IBS symptoms was seen in both group and individual hypnotherapy, and there was no significant difference in outcomes between the delivery of therapy based on patient IBS-SSS ($p = 0.16$) [48].

The ACG and BSG both recommend psychotherapies for IBS treatment; however, there is a noted low quality of evidence [16,17]. As a limiting factor, the ACG cites a lack of clinical trials using psychotherapies in isolation [16]. The BSG recommends psychotherapies be considered when symptoms have not improved after 12 months of drug treatment, suggesting that they should not be considered for first-line therapy [17]. Additionally, psychotherapies are not recommended for patients with underlying psychiatric conditions causing emotional instability [16]. Nonetheless, psychotherapies are overall very low risk for serious adverse effects and can particularly be a promising treatment option for IBS-M for which therapies are limited [16].

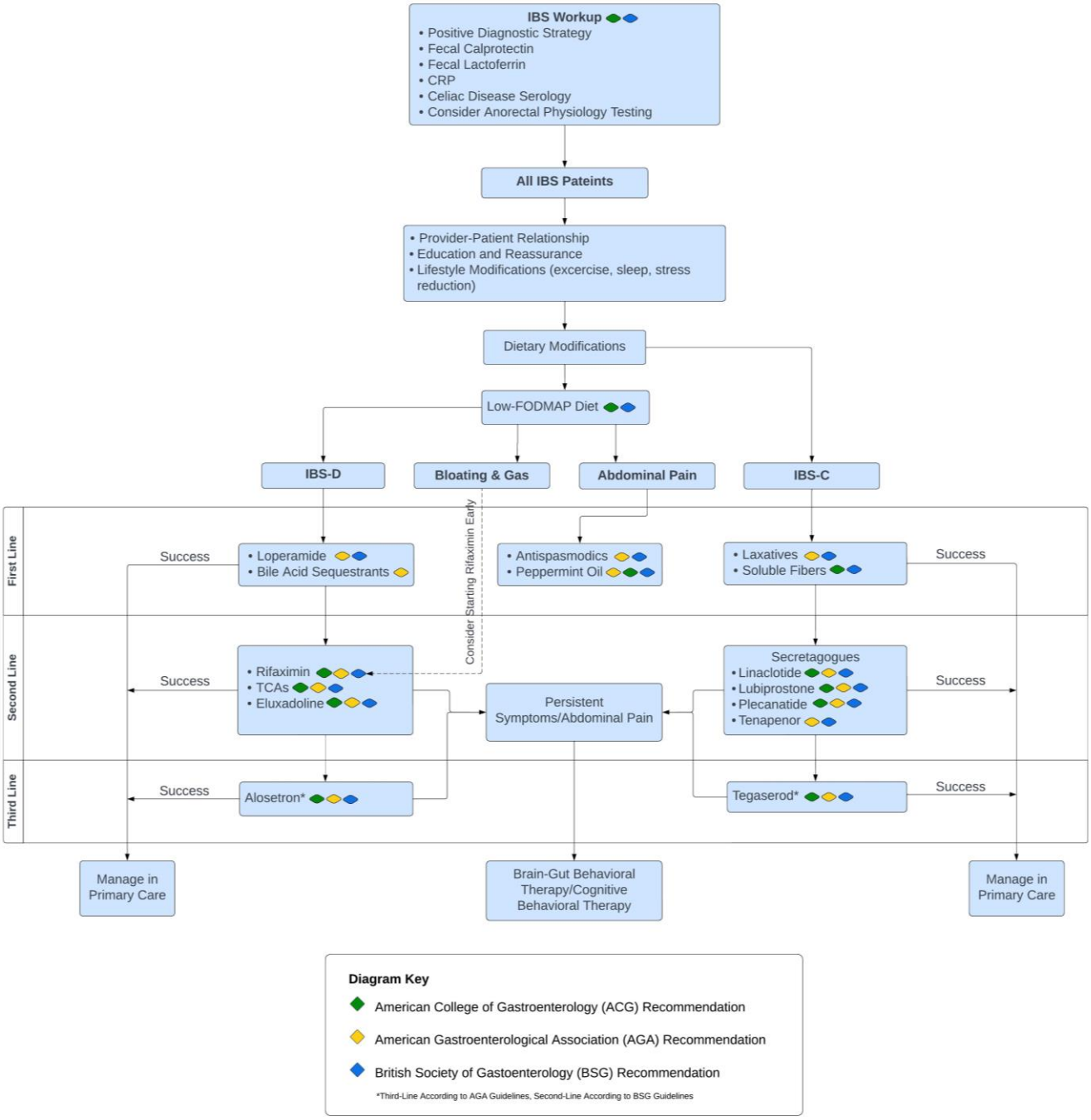

Figure 1. Aggregated Societal Diagnostic and Treatment Algorithm for IBS. As adapted from the American College of Gastroenterology (ACG) [16], American Gastroenterological Association (AGA) [49–51], and British Society of Gastroenterology (BSG) [17] treatment algorithms and guidelines.

3.3. IBS Abdominal Pain and Global Symptom Management

3.3.1. Antispasmodics

Broadly, antispasmodics relax gastrointestinal smooth muscle and may reduce visceral hypersensitivity; thereby, they have a potential role in alleviating global IBS symptoms and abdominal pain. The BSG weakly recommends their use for treating global symptoms and abdominal pain, whereas the ACG recommends against the use of antispasmodics currently available in the United States (dicyclomine, hyoscyamine, scopolamine) [16,17]. The American Gastroenterological Association (AGA) conditionally recommends their use [50]. The overall quality of the evidence is low (Table 2).

Table 2. Summary of Pharmacologic Agents and Supplements Used in the Management of IBS.

Drug	IBS Subtype	Mechanism of Action	FDA Approval	AGA Recommendation [50–52]	ACG Recommendation [16]	BSG Recommendation [17]
Antispasmodics	Global IBS symptoms and abdominal pain	Relax smooth muscle to decrease visceral hypersensitivity	Not specifically for IBS treatment	• Conditionally recommends use in IBS. • Low certainty	• Does not recommend the use of antispasmodics currently available in the United States (dicyclomine, hyoscyamine, scopolamine). • Low quality of evidence	• Weakly recommends use in global symptoms and abdominal pain in IBS. • Very low quality of evidence
Peppermint Oil	Global IBS symptoms and abdominal pain	L-methanol relaxes smooth muscle via calcium channel inhibition	Listed as generally safe	N/A	• Conditionally recommends use in global IBS symptoms. • Low quality of evidence	• Weakly recommends use in global symptoms and abdominal pain in IBS. • Very low quality of evidence
Probiotics	Global IBS symptoms and abdominal pain	Live microorganism strains that impact the gut microbiome	No	• No recommendations due to the knowledge gap.	• Suggests against use in global IBS symptoms. • Very low level of evidence	• Suggests may be effective for global symptoms and abdominal pain. • Very low quality of evidence
Loperamide	IBS-D	μ-opioid receptor agonist	Yes	• Conditionally recommends use in patients with IBS-D. • Very low certainty	• Does not recommend as first-line therapy in patients with IBS-D. • Moderate quality of evidence	• Strongly recommends use in patients with IBS-D. • Very low quality of evidence
Bile Acid Sequestrants	IBS-D	Reduction of bile acids in the gut to decrease bile acid malabsorption	Yes	N/A	• Does not recommend use in patients with IBS-D, conditional recommendation. • Very low quality of evidence	N/A
Rifaximin	IBS-D	Non-systemic, oral antibiotic altering gut microbiome	Yes	• Conditionally recommends use in patients with IBS-D. • Moderate certainty	• Strongly recommends use in patients with IBS-D. • Moderate level of evidence	• Weakly recommends use in patients with IBS-D. • Moderate quality of evidence
Eluxadoline	IBS-D	μ- and κ- opioid receptor agonist, δ-opioid receptor antagonist	Yes	• Conditionally recommends use in patients with IBS-D.	• Conditionally recommends use in patients with IBS-D. • Moderate quality of evidence	• Weakly recommends use in patients with IBS-D. • Moderate quality of evidence

Table 2. *Cont.*

Drug	IBS Subtype	Mechanism of Action	FDA Approval	AGA Recommendation [50–52]	ACG Recommendation [16]	BSG Recommendation [17]
Eluxadoline	IBS-D	μ- and κ- opioid receptor agonist, δ-opioid receptor antagonist	Yes	• Contraindicated for patients without a gallbladder or those who drink more than three alcoholic beverages daily. • Moderate certainty		
Tricyclic Antidepressants	IBS-D	Serotonin transporter (SERT) and norepinephrine transporter (NET) inhibition	Yes	• Conditionally recommends use in patients with IBS. • Low certainty	• Strongly recommends use in patients with IBS. • Moderate quality of evidence	• Strongly recommends use in patients with global IBS symptoms. • Moderate quality of evidence
Alosetron	IBS-D	Selective 5-HT_3 antagonist	Yes	• Conditionally recommends use in women with severe IBS-D who have not responded to conventional therapy. • Moderate certainty	• Conditionally recommends use in patients with IBS-D who have failed conventional therapy. • Low quality of evidence	• Weakly recommends use in patients with IBS-D. • Moderate to high quality of evidence
Lubiprostone	IBS-C	Chloride channel activator	Yes	• Conditionally recommends use in patients with IBS-C. • Moderate certainty	• Strongly recommends use in patients with IBS-C. • Moderate quality of evidence	• Strongly recommends use in patients with IBS-C. • Moderate quality of evidence
Linaclotide	IBS-C	Guanylate cyclase-C agonist	Yes	• Strongly recommends use in patients with IBS-C. • High certainty	• Strongly recommends use in patients with IBS-C. • High quality of evidence	• Strongly recommends use in patients with IBS-C. • High quality of evidence
Plecanatide	IBS-C	Guanylate cyclase-C agonist	Yes	• Conditionally recommends use in patients with IBS-C. • Moderate certainty	• Strongly recommends use in patients with IBS-C. • High quality of evidence	• Strongly recommends use in patients with IBS-C. • High quality of evidence
Tenapanor	IBS-C	NHE3 inhibitor	Yes	• Conditionally recommends use in patients with IBS-C. • Moderate certainty	N/A	• Strongly recommends use in patients with IBS-C. • High quality of evidence

Table 2. *Cont.*

Drug	IBS Subtype	Mechanism of Action	FDA Approval	AGA Recommendation [50–52]	ACG Recommendation [16]	BSG Recommendation [17]
Tegaserod	IBS-C	5-HT_4 agonist	Yes (Women <65-years-old)	• Conditionally recommends use in women < 65 years without history of cardiovascular ischemic events. • Moderate certainty	• Conditionally recommends use in women with IBS-C < 65 years without • cardiovascular risk factors who have not adequately responded to secretagogues. • Low quality of evidence	• Strongly recommends use in patients with IBS-C. • Moderate quality of evidence
Olorinab	IBS-D/IBS-C	Cannabinoid receptor-2 agonist	Currently in phase II trials	N/A	N/A	N/A
Dextofisopam	IBS-D/IBS-M	Modulation of autonomic function	Currently in phase II trials	N/A	N/A	N/A
MRx1234	IBS-M	Live biotherapeutic that competes with sulfate-reducing bacteria in the gut	Currently in phase II trials	N/A	N/A	N/A

A 2011 Cochrane review of 29 studies evaluating antispasmodic therapy in a total of 2,333 IBS patients found a significant benefit to antispasmodic treatment versus placebo in improving abdominal pain and global symptoms. Specifically in subgroup analysis, there was a significant benefit to cimteropium/dicyclomine, peppermint oil, pinaverium, and trimebutine [53]. A 2012 systematic review and meta-analysis by Martínez-Vázquez, et al., looking at antispasmodic agents available in Mexico (pinaverium bromide, mebeverine, otilonium, trimebutine, alverine, hyoscine, alverine/simethicone, pinaverium/simethicone, fenoverine, dicyclomine) in 27 clinical trial studies, found that antispasmodics were superior to placebo in IBS treatment and had limited adverse events [54]. The analysis found improvement in global symptoms (OR = 1.55; 95% CI 1.33–1.83), specifically with otilonium and alverine/simethicone. Pain improvement with antispasmodic therapy was also superior to placebo (OR = 1.52; 95% CI 1.28–1.80) [54].

Dicyclomine's efficaciousness has been studied and supported in limited older trials; a clinical trial by Page, et al. evaluated dicyclomine 40 mg four times daily over a two-week period in IBS patients, finding treatment to be superior to placebo in reducing abdominal pain and tenderness and in improving global condition and bowel habits [55]. Data on hyoscyamine use in IBS management are quite limited; one decades-old Swedish study cited by the ACG evaluated hyoscyamine 0.2 mg in 25 patients over two weeks, finding no significant response difference compared to placebo [16]. Scopolamine (hyoscine butylbromide) was combined with lorazepam and ispaghula husk in 12 blocks of eight patients in a double-blinded, placebo-controlled trial by Ritchie and colleagues. It was found in the study that scopolamine treatment alone led to no significant difference in subjective patient ratings versus placebo. However, there was significant improvement with combined ispaghula husk and scopolamine treatment ($p < 0.02$), and treatment with all three agents had an even greater effect ($p < 0.005$) [56].

Societal recommendations are discordant regarding the use of antispasmodics in IBS, and guidelines may largely be dependent on the agents available in their respective countries. Much of the currently available evidence is rather dated, and the quality is low; updated, larger clinical trials are needed to improve guidelines on the use of antispasmodics in this population.

3.3.2. Peppermint Oil

Peppermint oil is an over-the-counter herbal remedy that has antispasmodic properties; its L-methanol component relaxes bowel smooth muscle via calcium channel inhibition [16]. Its use is suggested by the ACG and weakly recommended by the BSG for the management of global IBS symptoms and abdominal pain. The quality of evidence is noted to be low [16,17] (Table 2).

A systematic review and meta-analysis by Khanna, et al. of nine randomized, placebo-controlled clinical trials of peppermint oil treatment for at least two weeks found that treatment significantly improved global IBS symptoms (RR = 2.23; 95% CI 1.78–2.81) and abdominal pain (RR = 2.14; 95% CI 1.64–2.79) compared to placebo. The most commonly reported adverse event was heartburn [57]. Conversely, a recent randomized, double-blinded trial by Weerts, et al. of patients with IBS treated with 182 mg small-intestinal-release peppermint oil, 182 mg ileocolonic-release peppermint oil, or placebo over eight weeks found no significant effects of either type of peppermint oil in reducing abdominal pain or in global symptom relief [58]. However, an updated meta-analysis by Black, et al. of eight randomized controlled trials, including the Weerts, et al. trial, still supported peppermint oil as being efficacious in relieving global symptoms compared to placebo [59]. The variability, as noted by Black and colleagues, may be due to improved methodology reporting by Weerts, et al. Additionally, this was the only peppermint oil trial to date to use U.S. Food and Drug Administration (FDA) and European Medicines Agency endpoints in evaluating efficacy [59].

Black, et al. highlight that many of the existing trials use specific oil formulations; thus, results cannot be generalized to the variety of products on the market [59]. Given the

overall poor safety regulation of commercially available peppermint oils, lack of quality studies, and heterogeneity in the available literature, more investigation is needed to improve best-practice guidelines. Nevertheless, peppermint oil is reported in studies as well-tolerated and can be considered in managing IBS symptoms.

3.3.3. Probiotics

There is increasing support in the literature for the role of the gut microbiome in IBS. As was previously discussed, post-infectious IBS suggests a temporal connection between acute gastroenteritis and subsequent development of IBS via microbiome changes [60]. Studies have delineated the differences in the microbiome between those with IBS and controls, such as decreased colonization of *Lactobacillus*, *Bifidobacterium*, and *F. prausnitzii* [61]. The influence of this microbial dysbiosis has been shown in rat models, in which inoculation of germfree rats with fecal samples from IBS patients led to increased abdominal contractions after colorectal distention, indicating transferred visceral hypersensitivity [62]. The successful use of antibiotics, prominently rifaximin, in IBS treatment further highlights the importance of the microbiome in the condition's pathophysiology [60]. Thus, the potential use of probiotics to address this dysbiosis remains in question.

A meta-analysis performed by Didari, et al. supported an improvement in abdominal pain score (RR = 1.96; 95% CI 1.14–3.36; $p = 0.01$) and global symptom score (RR = 2.43; 95% CI 1.13–5.21; $p = 0.02$); however, the analysis did not differentiate between the type of probiotic or IBS subtype [63]. Another meta-analysis by Ford, et al. found a significant positive effect on symptoms (RR = 0.79; 95% CI 0.68–0.91), but further analysis indicated heterogeneity and publication bias. With regard to abdominal pain and global symptoms, *Lactobacillus* and *Bifidobacterium* individually did not yield a significant difference compared to placebo. Analysis of studies that used a combination of probiotics did show improved symptom scores (SMD −0.31; 95% CI −0.44 to −0.17), with some potential for bias (Egger test, $p = 0.06$) [64].

The BSG acknowledges that probiotics can be effective in treating global symptoms and abdominal pain, suggesting a trial of up to 12 weeks, but asserts recommending a specific type is not possible with the current evidence [17]. The AGA makes no recommendation due to knowledge gaps, and the ACG recommends against its use for global symptoms [16,52]. Much of the current evidence is heterogeneous and of low quality, and the large variety of available probiotic combinations contributes to the difficulty in making standardized recommendations. Greater research is certainly needed to inform evidence-based guidelines on the implementation of probiotics in IBS management.

3.4. IBS-D Pharmacologic Management

There are currently three drugs approved for the treatment of IBS-D by the FDA: alosetron, rifaximin, and eluxadoline. Other existing agents that may be used in IBS-D are loperamide, neuromodulators, such as tricyclic antidepressants (TCAs), and bile acid sequestrants (Table 2).

3.4.1. Loperamide

Loperamide is a μ-opioid receptor agonist that delays gut transit time. It is an over-the-counter antidiarrheal agent that is commonly used in IBS-D. Unlike eluxadoline, loperamide has unopposed μ-opioid receptor agonism, lacking the attenuating effects of δ- opioid receptor antagonism [65].

There have been reported improvements in stool frequency, urgency, and consistency with loperamide. In a study by Cann, et al., loperamide had a significant positive effect on daily stool frequency ($p < 0.001$), passing unformed stools ($p < 0.01$), and urgency ($p < 0.001$) after five weeks of treatment in IBS patients [66]. On the other hand, a combined analysis of two randomized controlled trials of loperamide use in IBS-D and IBS-M patients (not including the Cann, et al. trial) found no statistically significant differences in loperamide versus placebo [67]. There is also limited evidence for improvement of IBS abdominal

pain and bloating with loperamide [68]. While the AGA and BSG recommend the use of loperamide in IBS-D, particularly for treating the symptoms of diarrhea, the ACG does not currently recommend its use as a first-line therapy [16,17,51].

3.4.2. Bile Acid Sequestrants

In a systematic review, the prevalence of bile acid malabsorption (BAM) in IBS-D patients was reported as 28.1% via pooled analysis [69]. A study by Wong and colleagues measured serum 7α-hydroxy-4-cholesten-3-one (reflection of bile acid synthesis) and stool bile acid concentration, finding that IBS-D patients synthesized and secreted more bile acids than those with IBS-C and those who were healthy [70]. It is even possible that those with idiopathic BAM have clinical features that are indistinguishable from IBS-D [69].

BAM may be due to a failure in reabsorption in the terminal ileum, leading to an increased load of bile acids in the colon. The bile acids then cause prosecretory effects that produce diarrhea, urgency, bloating, and abdominal pain/discomfort [69,71]. Specifically in the colon, the bile acids increase mucosal permeability, electrolyte and water secretion, and motility, all of which promote bile acid diarrhea [71].

A randomized, double-blinded, placebo-controlled study examining the use of bile acid sequestrant colesevelam (1875 mg twice a day) versus placebo in IBS-D patients found a significant increase in gut transit time with colesevelam (four hours longer for the ascending colon to empty), as well as a significantly greater reported ease in the passage of stool [72]. Another single-center, unblinded study with treatment of colesevelam (1875 mg twice a day) versus placebo in IBS-D patients found a significant increase in solid stools and an inverse relationship between bile acid sequestered in the stool and number of bowel movements within one week [73]. Therefore, bile acid sequestrants such as colesevelam may have utility in IBS-D treatment, especially given that more than a quarter of those with IBS-D can simultaneously have BAM.

3.4.3. Rifaximin

Rifaximin is a non-systemic, oral antibiotic with shown efficacy in adults with IBS-D. One of its proposed mechanisms is its ameliorating effects on the gut microbiome; however, a study by Fodor, et al. supported only limited and transient effects on the microbiome [74]. Therefore, the precise mechanism still requires further investigation.

In the TARGET clinical trials (two identical, phase III, double-blinded, placebo-controlled clinical trials), patients with IBS without constipation were given rifaximin (550 mg) or placebo three times a day for two weeks and then were followed post-treatment for 10 weeks. Adequate relief (defined as self-reported relief for at least two out of the first four weeks post-treatment) was assessed for global symptoms and, individually, abdominal pain, bloating, and stool consistency. Those treated with rifaximin had greater reported adequate relief of global IBS symptoms ($p < 0.001$, pooled from both trials) and bloating ($p < 0.001$, pooled from both trials) [75].

Repeat treatment with rifaximin has also been shown to be effective and well-tolerated, per a phase III, randomized, double-blinded, placebo-controlled trial conducted by Lembo, et al. Those who responded to a two-week trial of open-label rifaximin (550 mg three times a day) but relapsed in the following 18 weeks were randomized to receive a second rifaximin trial or placebo. There was a greater percentage of people with reduced abdominal pain in those who underwent a repeat trial ($p = 0.018$) versus placebo, as defined as a reduction in pain at least 30% from baseline for two of the first four weeks post-treatment. There was no significant difference with regard to stool consistency ($p = 0.42$) [76].

3.4.4. Eluxadoline

Eluxadoline is a μ- and κ-opioid receptor agonist and δ-opioid receptor antagonist that acts peripherally. Agonism of μ- and κ-opioid receptors slows down motility and decreases visceral pain sensation. Antagonism of δ-opioid receptors counterbalances the inhibitory

effects of μ-receptor agonism on gut contractility by promoting motor activity, thereby the antagonism allows for colonic motility that is more physiologic [65].

The first clinical trial of eluxadoline was a phase II study that randomly assigned adult patients with IBS-D to receive a placebo or 5, 25, 100, or 200 mg of eluxadoline twice a day over 12 weeks. Those receiving the 100 mg and 200 mg doses were significantly more likely versus placebo to meet the 2012 FDA endpoints with regard to stool consistency (daily Bristol stool scale less than type 5/no reported bowel movement for at least 50% of treatment days) and abdominal pain (reduction of at least 30% from baseline of mean daily worst abdominal pain score for at least 50% of treatment days) [77]. Two following phase III clinical trials conducted by Lembo, et al. also investigated the safety and efficacy of eluxadoline by randomly assigning adult patients with IBS-D to eluxadoline (75 mg or 100 mg) or placebo twice a day for 26 weeks (IBS-3002) or 52 weeks (IBS-3001). By week 12, more patients who received eluxadoline versus placebo reached the primary endpoint of improvement in stool consistency and abdominal pain in both trials [78]. Eluxadoline has also shown to be effective in patients who have failed previous trials of loperamide, another opioid receptor agonist [16,79,80].

Eluxadoline does have potential adverse effects of pancreatitis and sphincter of Oddi dysfunction; thus, its use is contraindicated in those without a gallbladder. It is also contraindicated in those with heavy alcohol use [78,81,82].

3.4.5. Tricyclic Antidepressants

Given the basis for gut–brain interactions in the pathophysiology of IBS and the psychiatric comorbidities in the disorder, neuromodulators such as TCAs can play a role in management. Bodies providing best practice guidelines, including the AGA and the BSG, recommend TCA use in IBS [17,51]. However, there is caution that the current certainty of the evidence of efficaciousness is moderate to low, and they are generally used as a second-line treatment option [16,17,51].

A meta-analysis performed by Xie, et al. of 12 randomized controlled trials of antidepressant use in IBS, six of which involved TCA use, found that there was a significant improvement in global symptoms (RR = 1.36; 95% CI 1.07–1.71) with TCAs [83]. This is congruent with an analysis performed by the AGA of eight randomized controlled trials, the majority of which enrolled IBS patients of different subtypes; they found that there was a significant improvement in global symptoms (RR = 0.67; 95% CI 0.54–0.82) and abdominal pain (RR = 0.76; 95% CI 0.61–0.94), but the quality of evidence was noted to be low [51]. Greater adverse events have been reported in IBS patients treated with TCAs versus placebo, commonly dry mouth and drowsiness [81]. TCAs increase gut transit times; the side effect of constipation overall may make TCAs more effective in treating IBS-D compared to other subtypes with more predominant constipation [81]. Yet, the effects of TCAs based on the predominant stool pattern have not been well-studied. One study by Vahedi, et al. did examine the effects of amitriptyline in just IBS-D, finding a significant reduction in reported loose stools and feelings of incomplete defecation with treatment [84].

3.4.6. Alosetron

Alosetron is a selective 5-HT_3 antagonist with a primary indication for women with severe, chronic IBS-D that has been refractory to other treatment options [85]. While the drug was initially withdrawn due to concerns of ischemic colitis and constipation, it has since been reintroduced in markets [65]. According to an analysis over nine years (2002–2011), the incidence of ischemic colitis remained stable, and the incidence of constipation declined [86].

Studies have supported the efficacy of using alosetron to treat IBS-D in this specific population. For example, Camilleri, et al. conducted a randomized controlled trial of women with IBS-D treated with 1 mg alosetron versus placebo twice a day for 12 weeks and found significant relief of pain and discomfort, as well as reduction in stool frequency and urgency. The most commonly reported adverse event from this study was constipation [87].

Another open-label, 12-week, multi-center study of women with moderate-to-severe IBS-D treated with 0.5 mg twice a day alosetron (dose escalation to 1 mg twice a day after four weeks if tolerated) found a significant improvement in symptoms. A total of 45% of patients enrolled met endpoints of reduced abdominal pain severity (30% decrease from baseline for weekly average of worst abdominal pain in the last 24 hours) and improvement in stool consistency (at least 50% reduction from baseline of number of days per week with at least one stool of Bristol Stool Scale type 6 or type 7). No adverse events of ischemic colitis or constipation were reported [85].

3.5. IBS-C Pharmacologic Management

Laxatives may have utility in IBS-C treatment. There are additionally five FDA-approved drugs for the treatment of IBS-C: lubiprostone, linaclotide, plecanatide, tegaserod, and tenapanor. The primary action of these medications is to improve symptoms of constipation by increasing fluid efflux into the intestinal lumen (Table 2).

3.5.1. Laxatives

Laxatives are often indicated in the treatment of constipation and are currently recommended by the AGA as a first-line treatment for IBS-C (Table 3). Osmotic laxatives, including polyethylene glycol, lactulose, magnesium citrate, and sodium phosphate, work similarly to soluble fiber by drawing water into the gut lumen and increasing stool propulsion [88]. Simulant laxatives, such as bisacodyl and senna, work by inducing colonic contractions and are frequently used as rescue agents when bowel movements have not occurred for two to three days [88]. Relief of constipation in IBS-C through laxatives in theory could be viable for symptom relief [16]. Clinical trials have shown that the use of laxatives, such as polyethylene glycol, may improve stool quality, but symptom relief has not been supported with significance [16].

Table 3. Summary of Types of Laxatives in the Management of IBS.

Laxatives	Mechanism of Action	Origin	Common Brands
Polyethylene glycol	Osmotic load draws water into the gastrointestinal lumen.	Derived from petroleum	MiraLAX, GoLytely, Glycolax
Bisacodyl	Stimulates enteric neurons to promote peristalsis.	Synthetic compound	Dulcolax, Ducodyl
Senna	Stimulates peristalsis and increases water in the gastrointestinal lumen.	Derived from dried leaflets or fruits of Cassia senna (*C. acutifolia*)	Senokot, Senna Lax, Ex-Lax, Senexon
Docusate sodium	Lowers the surface tension between feces and water, allowing lipids to enter and soften stool.	Synthetic compound	Colace, Dulcolax Stool Softener
Lactulose	Osmotic load draws water into the gastrointestinal lumen. Primarily used for decreasing intestinal ammonia in hyperammonemia from hepatic encephalopathy.	Derived from lactose	Unavailable over-the-counter

The largest clinical trial that investigated laxatives as an intervention for IBS-C was conducted by Chapman, et al. In this trial, polyethylene glycol was compared with placebo for patients with IBS-C. Regarding stool quality, results showed a significantly greater mean number of spontaneous bowel movements per day in the treatment group (1.28 ± 0.912 to 4.40 ± 2.581) compared with the placebo group (1.37 ± 0.849 to 3.11 ± 1.937) ($p < 0.0001$) [89]. However, abdominal pain, measured as a secondary endpoint in this trial, was not significantly reduced compared to placebo [89]. Conclusions drawn from this trial, along with the lack of substantial evidence following prior systematic reviews, have the ACG guidelines not currently recommending the use of polyethylene glycol to relieve

symptoms in patients with IBS-C [16]. Additionally, there are no current clinical trials that are investigating the use of other laxatives for the treatment of IBS-C, making their benefit in symptom relief uncertain [8,90].

3.5.2. Lubiprostone

Lubiprostone is a bicyclic fatty acid derivative of prostaglandin E1 (PGE1). It is a chloride channel activator that binds specifically to chloride channel 2 (ClC-2) and cystic fibrosis transmembrane conductance regulator (CFTR) channels, which can be abundantly found along the gastrointestinal tract [91]. These channels play an important role in transporting chloride (Cl) ions and fluid across the apical epithelial membranes for the purpose of secreting fluid into the gut lumen [92]. While it was originally thought that activating ClC-2 receptors on the apical surface of the intestinal epithelium contributes to the efflux of fluid and Cl ions, recent studies have shown that the receptor is primarily located on the basolateral side of the lumen, suggesting more of an absorption role as opposed to secretion. It is thought that lubiprostone exposure to these channels leads to the internalization of basolateral ClC-2 receptors, preventing absorption of Cl and keeping it in the gut lumen [91]. Lubiprostone's effects on CFTR channels contribute to the increased ion and fluid efflux. The drug acts on prostaglandin E2 receptor 4 (EP4) to increase the secretion of chloride through CFTR channels [91].

In a four-week, multi-center, parallel-group, double-blinded controlled trial conducted by Johanson, et al., lubiprostone treatment led to significant improvements in stool consistency, straining, constipation severity, and patient-reported assessments of treatment effectiveness compared to placebo at all weeks ($p < 0.0003$) [93]. Additionally, those treated with lubiprostone reported an increased number of spontaneous bowel movements at one week compared to the placebo group (5.69 vs. 3.46, $p = 0.0001$), with a greater frequency of spontaneous bowel movements reported at weeks two, three, and four ($p < 0.002$). This also included improvements in abdominal bloating and discomfort and global symptom relief. Lubiprostone showed a favorable safety profile in this trial, with the two most reported adverse events being nausea and headache [93].

3.5.3. Linaclotide

Linaclotide is an analogue of uroguanylin; it acts on the guanylate cyclase-C (GC-C) receptor and induces intestinal chloride and fluid secretion through the generation of cyclic guanosine monophosphate. This signal transduction subsequently activates multiple ion channels, such as CFTR and the Na-H ion exchanger, on the apical membrane surfaces [8]. This is followed by an efflux of sodium and water into the intestinal lumen.

In a meta-analysis performed by Atluri, et al., linaclotide was shown to be moderately effective compared with placebo in improving typical symptoms of IBS-C. These included improvements in abdominal pain or discomfort, global symptom relief, and clinically meaningful improvements in IBS-QoL (IBS quality of life survey) [94]. In addition, Rao, et al. conducted two phase III clinical trials in the treatment of IBS-C with linaclotide at 290 µg once daily for 12 weeks compared to placebo. In patients with severe IBS-C symptoms (bloating, fullness, discomfort, pain, cramping), linaclotide improved global symptoms ($p < 0.0001$) and IBS-QoL scores ($p < 0.01$) [95]. Similarly, in a multi-center, randomized, double-blinded, placebo-controlled trial of patients with IBS-C conducted by Johnston et al., linaclotide was given at various doses of 75–600 µg once daily for 12 weeks and was shown to significantly improve bowel habits at all doses [96]. The primary endpoint in this trial was a change in complete spontaneous bowel movement (CSBM) rates. The rate post-treatment was 2.90, 2.29, 3.61, and 2.68 for linaclotide doses of 76, 150, 300, and 600 µg, respectively, compared to 1.01 for placebo ($p < 0.01$ for each dose). In these studies, the most common adverse effect was diarrhea, which was dose-dependent and the main cause of patient discontinuation [96].

3.5.4. Plecanatide

Similar to linaclotide, plecanatide is also an analogue of uroguanylin and acts on GC-C receptors. It is a more novel agent that was recently FDA-approved for the management of IBS-C at 3-6 mg daily. In comparison to linaclotide, it is more pH sensitive and has a higher affinity for the GC-C receptor's acidic environment [97]. Like linaclotide, plecanatide promotes bowel transit and increases the amount of fluid in the gut lumen, which softens the stool. Two identical 12-week randomized, double-blinded, placebo-controlled trials showed similar efficacy of plecanatide. Plecanatide demonstrated improvement in abdominal pain (RR = 0.86; 95% CI 0.81–0.92) with a risk difference of 10.1% and CSBM (RR = 0.84; 95% CI 0.79–0.91) with a risk difference of 10.9%. In these trials, plecanatide led to significant improvements in stool consistency, stool frequency, straining, bloating, cramping, discomfort, and fullness [97]. Treatment was met with minimal associated side effects, primarily diarrhea, and a high level of tolerability. These reductions in IBS-C symptoms were congruent with observed treatment satisfaction and desire to continue treatment [97].

3.5.5. Tenapanor

Tenapanor is a newer agent in the treatment of IBS-C. It is a small molecule inhibitor of the sodium/hydrogen exchanger isoform 3 (NHE3) that is expressed on the apical surface of the small intestine and colon [98]. By inhibiting NHE3, tenapanor reduces sodium absorption and increases sodium and fluid excretion in the stool, promoting colonic fluid retention and a softer stool. This is in contrast with other secretagogues which promote direct secretion of ions across the apical membrane [98].

Tenapanor received FDA approval in 2019 following an excellent safety profile and compelling evidence of efficacy from large-scale phase III clinical trials. Two pivotal clinical trials conducted by Chey, et al., T3MP0-1 and subsequently T3MP0-2, demonstrated its efficacy [99]. T3MP0-2 was a multi-center, randomized, double-blinded, placebo-controlled trial conducted in patients with IBS-C receiving tenapanor at 50 mg twice a day or placebo twice a day for 26 weeks. Treatment with tenapanor significantly improved IBS-C symptoms—an increase in the frequency of CSBM and a reduction in abdominal symptoms (discomfort, bloating, cramping, fullness) for more than 13 weeks of the 26-week treatment period. Patients receiving tenapanor reported a significant improvement from baseline in treatment satisfaction at week 26 compared with placebo; 80.5% of patients receiving tenapanor were at least moderately satisfied with their treatment compared with 61.2% of patients receiving placebo [99].

Tenapanor has minimal systemic availability and minimal adverse events. Diarrhea was the most reported adverse event of tenapanor across the two trials, with abdominal distension, flatulence, and dizziness also occurring [99]. Severe diarrhea occurred in 2.5% of tenapanor-treated patients versus 0.2% of placebo-treated patients [100]. While a promising new drug, the cost dynamics may be the driving factor in the usage of this treatment clinically [98].

3.5.6. Tegaserod

One interesting class of IBS-C medications includes serotonin agonists. There is one FDA-approved drug named tegaserod that is not without controversy. Tegaserod works as a 5-HT_4 receptor agonist that stimulates motility and increases fluid efflux into the gastrointestinal lumen [50]. It is a prokinetic that stimulates propulsive motility and has been explored as a potential treatment for several disorders involving hypomotility secondary to altered gut–brain interactions. It was originally approved by the FDA in 2002 for short-term treatment of IBS-C and had success in phase II/III clinical trials. Two pivotal 12-week placebo-controlled studies were conducted prior to approval; one trial evaluated doses of 2 mg and 6 mg in both men and women, and one trial evaluated 6 mg twice daily in women [101]. High responder rates in these trials led to its initial approval at 6 mg twice daily for women with IBS-C [101].

Additional data from these trials, as summarized by the AGA, showed greater symptom relief using the FDA responder endpoint for IBS-C (RR = 0.87; 95% CI 0.81–0.93). Tegaserod was also associated with improvement in bowel movement frequency in 65.6% of patients receiving the drug versus 51.2% of patients receiving a placebo (RR = 0.71; 95% CI 0.65–0.77) over 12 weeks of treatment [50,101]. Finally, compared with placebo, the mean difference in overall IBS-QoL score from baseline to week 12 was an increase of 1.21 points with tegaserod (95% CI −0.76–3.18) [50,101].

However, following these trials, it was subsequently withdrawn from the market due to a retrospective analysis of clinical trials that showed a higher rate of cardiovascular ischemic events. A systematic review conducted by Tack, et al. analyzed the safety profile of various 5-HT_4 agonists developed for gastrointestinal disorders, including tegaserod. In three randomized, double-blinded, placebo-controlled, parallel-group clinical trials, 13 of 11,614 patients treated with tegaserod had adverse cardiovascular effects (myocardial infarction, unstable angina pectoris, stroke, and one sudden death) at a rate of 0.11% compared to 1 of 7,031 patients treated with placebo at a rate of 0.01%. These findings led to its withdrawal [102]. Following its withdrawal, additional safety data were collected, and resubmission to the FDA in 2019 led to its reapproval for the treatment of IBS-C with conditions that the treatment population be limited to women under the age of 65 years without heart disease (unstable angina, myocardial infarction, stroke, transient ischemic attack) or other underlying cardiovascular risk factors (active smoking, hypertension, hypercholesterolemia, diabetes mellitus, obesity) [101]. Thus, tegaserod may be a viable option for women who have not responded well to other standard treatments.

4. Recent Advancements in IBS Pharmacology

4.1. Olorinab

The cannabinoid receptor 2 (CB_2) is expressed in the enteric system, and those with IBS have increased expression in their colonic mucosa [103,104]. CB_2 agonists have shown promise in reducing visceral pain in rat models [105]. Olorinab is a peripherally acting selective agonist of CB_2 that has most recently undergone a phase IIb, randomized, double-blinded, placebo-controlled clinical trial for IBS abdominal pain.

Subjects with IBS-D or IBS-C via Rome IV criteria were given olorinab at 10 mg, 25 mg, or 50 mg versus placebo three times a day for 12 weeks. Weekly average abdominal pain score (AAPS) was assessed throughout the 12 weeks. Olorinab experimental groups failed to significantly meet the primary endpoint of change in AAPS from baseline to week 12. A prespecified analysis of subjects with baseline AAPS $\geq$ 6.5, however, showed a significant reduction in weekly AAPS for the 50 mg dose compared to placebo for those with IBS-C but not IBS-D [106]. While olorinab works to target a novel mechanism potentially underlying abdominal pain in IBS, more research and development are needed for cannabinoid receptor agonists considering the primary endpoint was not met in this clinical trial.

4.2. Dextofisopam

Dextofisopam is a benzodiazepine and an R-enantiomer of tofisopam, a nonsedating agent used for a variety of illnesses associated with autonomic instability. It is thought that modulation of autonomic function, including gastrointestinal motor and sensory activity, can help relieve symptoms of IBS-M. Dextofisopam binds to novel sites in the central nervous system that are concentrated in the subcortical ganglia, substantia nigra, and hypothalamus, compared to classic benzodiazepine binding sites that are primarily located in the cortical area [107].

One phase II, randomized, double-blinded, placebo-controlled, parallel-group trial was conducted to assess efficacy, safety, and tolerability at a dose of 200 mg twice a day in the treatment of both IBS-D and IBS-M. The results of this trial showed patients treated with dextofisopam exhibited decreased stool frequency and improved stool consistency. Over a treatment period of 12 weeks, there was a greater proportion of patients with adequate overall relief of IBS symptoms during the first month of treatment with dextofisopam

relative to placebo (73% vs. 49%; $p = 0.002$). However, the difference between treatment groups was not significant during the second month (56% vs. 43%; $p = 0.084$), which suggests further testing may be needed [107]. The onset of effect for dextofisopam was rapid, with a greater proportion of treated patients than placebo patients reporting adequate overall relief as early as the first week of treatment (57% vs. 33%; $p = 0.004$). The efficacy was also similar across genders and IBS subtypes, and it was shown to be safe and well-tolerated [107].

4.3. MRx1234

The FDA recently defined a new potential treatment option for IBS under the classification of live biotherapeutics [108]. These medications contain microorganisms but are distinct from probiotics due to high pharmaceutical expectations. One new and potential future treatment for IBS-M under this class is MRx1234 (*Blautix*), a live biotherapeutic containing a strain of *Blautia hydrogenotrophica*—a gram-positive, anaerobic, non-spore-forming coccobacillus. Based on animal models, its proposed mechanism of action is competing with sulfate-reducing bacteria in the gut, thereby reducing the production of gasses such as hydrogen, H_2S, and methane and normalizing the gut microbiome [108].

In a phase II multi-center, randomized, double-blinded, placebo-controlled, parallel-group clinical trial, the efficacy and safety of MRx1234 was measured across cohorts of IBS-D and IBS-C patients, with the idea that treatment would show benefit for both subtypes and offer future therapy for IBS-M. While the results for the primary endpoints of reported improvements in both bowel habit and abdominal pain showed promise for treatment versus placebo, they were not statistically significant (IBS-C cohort 25.0% vs. 17.1%, $p = 0.152$; IBS-D cohort 23.4% vs. 17.8%, $p = 0.216$). Yet, improvement in bowel habits showed statistical significance when both cohorts were combined (52.9% vs. 39.9%; $p = 0.007$). The most frequent, and possibly treatment-related, adverse events were diarrhea, abdominal pain, dyspepsia, and headache. The results of this trial showed that while further testing may be required, there is potential that this agent could be useful for patients with IBS-M, given its benefit with combined analysis of IBS-D and IBS-C patients [108].

5. Conclusions

This clinical review showcases diagnostic guidelines, standard treatments, and recent pharmacologic advancements in the management of IBS. The high prevalence of IBS and its impact on patient quality of life emphasize the importance of choosing a treatment option that fits the patient's clinical picture. The complex pathophysiology of IBS, distinct subtypes, and multitude of associated symptoms have spurred the development of treatments designed to target a variety of the disorder's processes. Therapeutic strategies can involve dietary modifications, psychotherapies, nonpharmacologic supplements, and pharmacologic agents. Many standard treatments offer specific relief to diarrhea-predominant and constipation-predominant forms of IBS. While there are currently no known approved therapies for IBS-M, there are promising medications on the rise and space for further research. As the development of newer agents progresses, there is hope that treatment options for IBS will expand and continue to improve.

Author Contributions: conceptualization, D.S.C., R.S.W. and M.T.; drafting of the manuscript, D.S.C. and R.S.W.; critical revision of the manuscript, D.S.C., R.S.W. and M.T.; supervision, M.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Black, C.J.; Ford, A.C. Global burden of irritable bowel syndrome: Trends, predictions and risk factors. *Nat. Rev. Gastroenterol. Hepatol.* **2020**, *17*, 473–486. [CrossRef] [PubMed]
2. Patel, N.; Shackelford, K. Irritable Bowel Syndrome. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2023.
3. Rome Foundation. *Rome IV Diagnostic Criteria for FGIDs*. Available online: https://theromefoundation.org/rome-iv/rome-iv-criteria/ (accessed on 20 June 2024).
4. Drossman, D.A.; Camilleri, M.; Mayer, E.A.; Whitehead, W.E. AGA technical review on irritable bowel syndrome. *Gastroenterology* **2002**, *123*, 2108–2131. [CrossRef] [PubMed]
5. Karantanos, T.; Markoutsaki, T.; Gazouli, M.; Anagnou, N.P.; Karamanolis, D.G. Current insights in to the pathophysiology of Irritable Bowel Syndrome. *Gut Pathog.* **2010**, *2*, 3. [CrossRef]
6. Tillisch, K.; Mayer, E.A.; Labus, J.S. Quantitative meta-analysis identifies brain regions activated during rectal distension in irritable bowel syndrome. *Gastroenterology* **2011**, *140*, 91–100. [CrossRef] [PubMed]
7. Oswiecimska, J.; Szymlak, A.; Roczniak, W.; Girczys-Poledniok, K.; Kwiecien, J. New insights into the pathogenesis and treatment of irritable bowel syndrome. *Adv. Med. Sci.* **2017**, *62*, 17–30. [CrossRef]
8. Saha, L. Irritable bowel syndrome: Pathogenesis, diagnosis, treatment, and evidence-based medicine. *World J. Gastroenterol.* **2014**, *20*, 6759–6773. [CrossRef]
9. Tian, C.M.; Zhang, Y.; Yang, M.F.; Xu, H.M.; Zhu, M.Z.; Yao, J.; Wang, L.S.; Liang, Y.J.; Li, D.F. Stem Cell Therapy in Inflammatory Bowel Disease: A Review of Achievements and Challenges. *J. Inflamm. Res.* **2023**, *16*, 2089–2119. [CrossRef]
10. Panes, J.; Garcia-Olmo, D.; Van Assche, G.; Colombel, J.F.; Reinisch, W.; Baumgart, D.C.; Dignass, A.; Nachury, M.; Ferrante, M.; Kazemi-Shirazi, L.; et al. Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: A phase 3 randomised, double-blind controlled trial. *Lancet* **2016**, *388*, 1281–1290. [CrossRef]
11. Dave, M.; Dev, A.; Somoza, R.A.; Zhao, N.; Viswanath, S.; Mina, P.R.; Chirra, P.; Obmann, V.C.; Mahabeleshwar, G.H.; Menghini, P.; et al. MSCs mediate long-term efficacy in a Crohn's disease model by sustained anti-inflammatory macrophage programming via efferocytosis. *NPJ Regen. Med.* **2024**, *9*, 6. [CrossRef]
12. El-Salhy, M. Possible role of intestinal stem cells in the pathophysiology of irritable bowel syndrome. *World J. Gastroenterol.* **2020**, *26*, 1427–1438. [CrossRef]
13. Wilkins, T.; Pepitone, C.; Alex, B.; Schade, R.R. Diagnosis and management of IBS in adults. *Am. Fam. Physician* **2012**, *86*, 419–426. [PubMed]
14. Werlang, M.E.; Palmer, W.C.; Lacy, B.E. Irritable Bowel Syndrome and Dietary Interventions. *Gastroenterol. Hepatol.* **2019**, *15*, 16–26.
15. Berry, S.K.; Chey, W.D. Integrated Care for Irritable Bowel Syndrome: The Future Is Now. *Gastroenterol. Clin. N. Am.* **2021**, *50*, 713–720. [CrossRef]
16. Lacy, B.E.; Pimentel, M.; Brenner, D.M.; Chey, W.D.; Keefer, L.A.; Long, M.D.; Moshiree, B. ACG Clinical Guideline: Management of Irritable Bowel Syndrome. *Am. J. Gastroenterol.* **2021**, *116*, 17–44. [CrossRef] [PubMed]
17. Vasant, D.H.; Paine, P.A.; Black, C.J.; Houghton, L.A.; Everitt, H.A.; Corsetti, M.; Agrawal, A.; Aziz, I.; Farmer, A.D.; Eugenicos, M.P.; et al. British Society of Gastroenterology guidelines on the management of irritable bowel syndrome. *Gut* **2021**, *70*, 1214–1240. [CrossRef] [PubMed]
18. Begtrup, L.M.; Engsbro, A.L.; Kjeldsen, J.; Larsen, P.V.; Schaffalitzky de Muckadell, O.; Bytzer, P.; Jarbol, D.E. A positive diagnostic strategy is noninferior to a strategy of exclusion for patients with irritable bowel syndrome. *Clin. Gastroenterol. Hepatol.* **2013**, *11*, 956–962.e951. [CrossRef]
19. Sayuk, G.S.; Wolf, R.; Chang, L. Comparison of Symptoms, Healthcare Utilization, and Treatment in Diagnosed and Undiagnosed Individuals With Diarrhea-Predominant Irritable Bowel Syndrome. *Am. J. Gastroenterol.* **2017**, *112*, 892–899. [CrossRef]
20. Menees, S.B.; Powell, C.; Kurlander, J.; Goel, A.; Chey, W.D. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. *Am. J. Gastroenterol.* **2015**, *110*, 444–454. [CrossRef]
21. van Rheenen, P.F.; Van de Vijver, E.; Fidler, V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: Diagnostic meta-analysis. *BMJ* **2010**, *341*, c3369. [CrossRef]
22. Zhou, X.L.; Xu, W.; Tang, X.X.; Luo, L.S.; Tu, J.F.; Zhang, C.J.; Xu, X.; Wu, Q.D.; Pan, W.S. Fecal lactoferrin in discriminating inflammatory bowel disease from irritable bowel syndrome: A diagnostic meta-analysis. *BMC Gastroenterol.* **2014**, *14*, 121. [CrossRef]
23. Irvine, A.J.; Chey, W.D.; Ford, A.C. Screening for Celiac Disease in Irritable Bowel Syndrome: An Updated Systematic Review and Meta-analysis. *Am. J. Gastroenterol.* **2017**, *112*, 65–76. [CrossRef] [PubMed]
24. Cash, B.D.; Rubenstein, J.H.; Young, P.E.; Gentry, A.; Nojkov, B.; Lee, D.; Andrews, A.H.; Dobhan, R.; Chey, W.D. The prevalence of celiac disease among patients with nonconstipated irritable bowel syndrome is similar to controls. *Gastroenterology* **2011**, *141*, 1187–1193. [CrossRef]
25. Chey, W.D.; Hashash, J.G.; 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. [CrossRef]

26. Spiegel, B.M.; Gralnek, I.M.; Bolus, R.; Chang, L.; Dulai, G.S.; Naliboff, B.; Mayer, E.A. Is a negative colonoscopy associated with reassurance or improved health-related quality of life in irritable bowel syndrome? *Gastrointest. Endosc.* **2005**, *62*, 892–899. [CrossRef] [PubMed]
27. Black, T.P.; Manolakis, C.S.; Di Palma, J.A. "Red flag" evaluation yield in irritable bowel syndrome. *J. Gastrointest. Liver Dis.* **2012**, *21*, 153–156. [CrossRef]
28. Mulak, A.; Paradowski, L. Anorectal function and dyssynergic defecation in different subgroups of patients with irritable bowel syndrome. *Int. J. Color. Dis.* **2010**, *25*, 1011–1016. [CrossRef]
29. Suttor, V.P.; Prott, G.M.; Hansen, R.D.; Kellow, J.E.; Malcolm, A. Evidence for pelvic floor dyssynergia in patients with irritable bowel syndrome. *Dis. Colon Rectum* **2010**, *53*, 156–160. [CrossRef]
30. Baker, J.; Eswaran, S.; Saad, R.; Menees, S.; Shifferd, J.; Erickson, K.; Barthelemy, A.; Chey, W.D. Abdominal Symptoms Are Common and Benefit from Biofeedback Therapy in Patients with Dyssynergic Defecation. *Clin. Transl. Gastroenterol.* **2015**, *6*, e105. [CrossRef] [PubMed]
31. Patcharatrakul, T.; Gonlachanvit, S. Outcome of biofeedback therapy in dyssynergic defecation patients with and without irritable bowel syndrome. *J. Clin. Gastroenterol.* **2011**, *45*, 593–598. [CrossRef]
32. Cozma-Petrut, A.; Loghin, F.; Miere, D.; Dumitrascu, D.L. Diet in irritable bowel syndrome: What to recommend, not what to forbid to patients! *World J. Gastroenterol.* **2017**, *23*, 3771–3783. [CrossRef]
33. Gibson, P.R.; Shepherd, S.J. Personal view: Food for thought--western lifestyle and susceptibility to Crohn's disease. The FODMAP hypothesis. *Aliment. Pharmacol. Ther.* **2005**, *21*, 1399–1409. [CrossRef] [PubMed]
34. Magge, S.; Lembo, A. Low-FODMAP Diet for Treatment of Irritable Bowel Syndrome. *Gastroenterol. Hepatol.* **2012**, *8*, 739–745.
35. Black, C.J.; Staudacher, H.M.; Ford, A.C. Efficacy of a low FODMAP diet in irritable bowel syndrome: Systematic review and network meta-analysis. *Gut* **2022**, *71*, 1117–1126. [CrossRef]
36. Bellini, M.; Tonarelli, S.; Nagy, A.G.; Pancetti, A.; Costa, F.; Ricchiuti, A.; de Bortoli, N.; Mosca, M.; Marchi, S.; Rossi, A. Low FODMAP Diet: Evidence, Doubts, and Hopes. *Nutrients* **2020**, *12*, 148. [CrossRef] [PubMed]
37. Staudacher, H.M. Nutritional, microbiological and psychosocial implications of the low FODMAP diet. *J. Gastroenterol. Hepatol.* **2017**, *32* (Suppl. 1), 16–19. [CrossRef]
38. Staudacher, H.M.; Lomer, M.C.; Anderson, J.L.; Barrett, J.S.; Muir, J.G.; Irving, P.M.; Whelan, K. Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. *J. Nutr.* **2012**, *142*, 1510–1518. [CrossRef]
39. El-Salhy, M.; Ystad, S.O.; Mazzawi, T.; Gundersen, D. Dietary fiber in irritable bowel syndrome (Review). *Int. J. Mol. Med.* **2017**, *40*, 607–613. [CrossRef]
40. Bijkerk, C.J.; Muris, J.W.; Knottnerus, J.A.; Hoes, A.W.; de Wit, N.J. Systematic review: The role of different types of fibre in the treatment of irritable bowel syndrome. *Aliment. Pharmacol. Ther.* **2004**, *19*, 245–251. [CrossRef]
41. Moayyedi, P.; Quigley, E.M.; Lacy, B.E.; Lembo, A.J.; Saito, Y.A.; Schiller, L.R.; Soffer, E.E.; Spiegel, B.M.; Ford, A.C. The effect of fiber supplementation on irritable bowel syndrome: A systematic review and meta-analysis. *Am. J. Gastroenterol.* **2014**, *109*, 1367–1374. [CrossRef]
42. Van Oudenhove, L.; Crowell, M.D.; Drossman, D.A.; Halpert, A.D.; Keefer, L.; Lackner, J.M.; Murphy, T.B.; Naliboff, B.D.; Levy, R.L. Biopsychosocial Aspects of Functional Gastrointestinal Disorders. *Gastroenterology* **2016**, *150*, 1355–1367. [CrossRef]
43. Lackner, J.M.; Jaccard, J.; Radziwon, C.D.; Firth, R.S.; Gudleski, G.D.; Hamilton, F.; Katz, L.A.; Keefer, L.; Krasner, S.S.; Ma, C.X.; et al. Durability and Decay of Treatment Benefit of Cognitive Behavioral Therapy for Irritable Bowel Syndrome: 12-Month Follow-Up. *Am. J. Gastroenterol.* **2019**, *114*, 330–338. [CrossRef] [PubMed]
44. Everitt, H.A.; Landau, S.; O'Reilly, G.; Sibelli, A.; Hughes, S.; Windgassen, S.; Holland, R.; Little, P.; McCrone, P.; Bishop, F.L.; 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*, 863–872. [CrossRef] [PubMed]
45. Jacobs, J.P.; Gupta, A.; Bhatt, R.R.; Brawer, J.; Gao, K.; Tillisch, K.; Lagishetty, V.; Firth, R.; Gudleski, G.D.; Ellingson, B.M.; 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. [CrossRef] [PubMed]
46. Whorwell, P.J.; Prior, A.; Faragher, E.B. Controlled trial of hypnotherapy in the treatment of severe refractory irritable-bowel syndrome. *Lancet* **1984**, *2*, 1232–1234. [CrossRef]
47. Flik, C.E.; Laan, W.; Zuithoff, N.P.A.; van Rood, Y.R.; Smout, A.; Weusten, B.; Whorwell, P.J.; de Wit, N.J. Efficacy of individual and group hypnotherapy in irritable bowel syndrome (IMAGINE): A multicentre randomised controlled trial. *Lancet Gastroenterol. Hepatol.* **2019**, *4*, 20–31. [CrossRef]
48. Lovdahl, J.; Tornblom, H.; Ringstrom, G.; Palsson, O.S.; Simren, M. Randomised clinical trial: Individual versus group hypnotherapy for irritable bowel syndrome. *Aliment. Pharmacol. Ther.* **2022**, *55*, 1501–1511. [CrossRef]
49. American Gastroenterological Association. *Clinical Decision Support Tool: IBS Treatment*; American Gastroenterological Association: Bethesda, MD, USA, 2022; Volume 163.
50. Chang, L.; Sultan, S.; Lembo, A.; Verne, G.N.; Smalley, W.; Heidelbaugh, J.J. AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome with Constipation. *Gastroenterology* **2022**, *163*, 118–136. [CrossRef]
51. Lembo, A.; Sultan, S.; Chang, L.; Heidelbaugh, J.J.; Smalley, W.; Verne, G.N. AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome with Diarrhea. *Gastroenterology* **2022**, *163*, 137–151. [CrossRef]

52. Su, G.L.; Ko, C.W.; Bercik, P.; Falck-Ytter, Y.; Sultan, S.; Weizman, A.V.; Morgan, R.L. AGA Clinical Practice Guidelines on the Role of Probiotics in the Management of Gastrointestinal Disorders. *Gastroenterology* **2020**, *159*, 697–705. [CrossRef]
53. Ruepert, L.; Quartero, A.O.; de Wit, N.J.; van der Heijden, G.J.; Rubin, G.; Muris, J.W. Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. *Cochrane Database Syst. Rev.* **2011**, *2011*, CD003460. [CrossRef]
54. Martinez-Vazquez, M.A.; Vazquez-Elizondo, G.; Gonzalez-Gonzalez, J.A.; Gutierrez-Udave, R.; Maldonado-Garza, H.J.; Bosques-Padilla, F.J. Effect of antispasmodic agents, alone or in combination, in the treatment of Irritable Bowel Syndrome: Systematic review and meta-analysis. *Rev. Gastroenterol. Mex.* **2012**, *77*, 82–90. [CrossRef] [PubMed]
55. Page, J.G.; Dirnberger, G.M. Treatment of the irritable bowel syndrome with Bentyl (dicyclomine hydrochloride). *J. Clin. Gastroenterol.* **1981**, *3*, 153–156. [CrossRef] [PubMed]
56. Ritchie, J.A.; Truelove, S.C. Treatment of irritable bowel syndrome with lorazepam, hyoscine butylbromide, and ispaghula husk. *Br. Med. J.* **1979**, *1*, 376–378. [CrossRef]
57. Khanna, R.; MacDonald, J.K.; Levesque, B.G. Peppermint oil for the treatment of irritable bowel syndrome: A systematic review and meta-analysis. *J. Clin. Gastroenterol.* **2014**, *48*, 505–512. [CrossRef] [PubMed]
58. Weerts, Z.; Masclee, A.A.M.; Witteman, B.J.M.; Clemens, C.H.M.; Winkens, B.; Brouwers, J.; Frijlink, H.W.; Muris, J.W.M.; De Wit, N.J.; Essers, B.A.B.; et al. Efficacy and Safety of Peppermint Oil in a Randomized, Double-Blind Trial of Patients With Irritable Bowel Syndrome. *Gastroenterology* **2020**, *158*, 123–136. [CrossRef] [PubMed]
59. Black, C.J.; Moayyedi, P.; Quigley, E.M.M.; Ford, A.C. Peppermint Oil in Irritable Bowel Syndrome. *Gastroenterology* **2020**, *159*, 395–396. [CrossRef]
60. Pimentel, M.; Lembo, A. Microbiome and Its Role in Irritable Bowel Syndrome. *Dig. Dis. Sci.* **2020**, *65*, 829–839. [CrossRef]
61. Liu, H.N.; Wu, H.; Chen, Y.Z.; Chen, Y.J.; Shen, X.Z.; Liu, T.T. Altered molecular signature of intestinal microbiota in irritable bowel syndrome patients compared with healthy controls: A systematic review and meta-analysis. *Dig. Liver Dis.* **2017**, *49*, 331–337. [CrossRef]
62. Crouzet, L.; Gaultier, E.; Del'Homme, C.; Cartier, C.; Delmas, E.; Dapoigny, M.; Fioramonti, J.; Bernalier-Donadille, A. The hypersensitivity to colonic distension of IBS patients can be transferred to rats through their fecal microbiota. *Neurogastroenterol. Motil.* **2013**, *25*, e272–e282. [CrossRef]
63. Didari, T.; Mozaffari, S.; Nikfar, S.; Abdollahi, M. Effectiveness of probiotics in irritable bowel syndrome: Updated systematic review with meta-analysis. *World J. Gastroenterol.* **2015**, *21*, 3072–3084. [CrossRef]
64. Ford, A.C.; Harris, L.A.; Lacy, B.E.; Quigley, E.M.M.; Moayyedi, P. Systematic review with meta-analysis: The efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. *Aliment. Pharmacol. Ther.* **2018**, *48*, 1044–1060. [CrossRef]
65. Liu, R.; Staller, K. Update on Eluxadoline for the Treatment of Irritable Bowel Syndrome with Diarrhea: Patient Selection and Perspectives. *Drug Des. Devel Ther.* **2020**, *14*, 1391–1400. [CrossRef] [PubMed]
66. Cann, P.A.; Read, N.W.; Holdsworth, C.D.; Barends, D. Role of loperamide and placebo in management of irritable bowel syndrome (IBS). *Dig. Dis. Sci.* **1984**, *29*, 239–247. [CrossRef] [PubMed]
67. Ford, A.C.; Moayyedi, P.; Chey, W.D.; Harris, L.A.; Lacy, B.E.; Saito, Y.A.; Quigley, E.M.M. American College of Gastroenterology Monograph on Management of Irritable Bowel Syndrome. *Am. J. Gastroenterol.* **2018**, *113*, 1–18. [CrossRef] [PubMed]
68. Lacy, B.E. Diagnosis and treatment of diarrhea-predominant irritable bowel syndrome. *Int. J. Gen. Med.* **2016**, *9*, 7–17. [CrossRef]
69. Slattery, S.A.; Niaz, O.; Aziz, Q.; Ford, A.C.; Farmer, A.D. Systematic review with meta-analysis: The prevalence of bile acid malabsorption in the irritable bowel syndrome with diarrhoea. *Aliment. Pharmacol. Ther.* **2015**, *42*, 3–11. [CrossRef]
70. Wong, B.S.; Camilleri, M.; Carlson, P.; McKinzie, S.; Busciglio, I.; Bondar, O.; Dyer, R.B.; Lamsam, J.; Zinsmeister, A.R. Increased bile acid biosynthesis is associated with irritable bowel syndrome with diarrhea. *Clin. Gastroenterol. Hepatol.* **2012**, *10*, 1009–1015.e3. [CrossRef]
71. Camilleri, M. Advances in understanding of bile acid diarrhea. *Expert Rev. Gastroenterol. Hepatol.* **2014**, *8*, 49–61. [CrossRef]
72. Odunsi-Shiyanbade, S.T.; Camilleri, M.; McKinzie, S.; Burton, D.; Carlson, P.; Busciglio, I.A.; Lamsam, J.; Singh, R.; Zinsmeister, A.R. Effects of chenodeoxycholate and a bile acid sequestrant, colesevelam, on intestinal transit and bowel function. *Clin. Gastroenterol. Hepatol.* **2010**, *8*, 159–165. [CrossRef]
73. Camilleri, M.; Acosta, A.; Busciglio, I.; Boldingh, A.; Dyer, R.B.; Zinsmeister, A.R.; Lueke, A.; Gray, A.; Donato, L.J. Effect of colesevelam on faecal bile acids and bowel functions in diarrhoea-predominant irritable bowel syndrome. *Aliment. Pharmacol. Ther.* **2015**, *41*, 438–448. [CrossRef]
74. Fodor, A.A.; Pimentel, M.; Chey, W.D.; Lembo, A.; Golden, P.L.; Israel, R.J.; Carroll, I.M. Rifaximin is associated with modest, transient decreases in multiple taxa in the gut microbiota of patients with diarrhoea-predominant irritable bowel syndrome. *Gut Microbes* **2019**, *10*, 22–33. [CrossRef] [PubMed]
75. Pimentel, M.; Lembo, A.; Chey, W.D.; Zakko, S.; Ringel, Y.; Yu, J.; Mareya, S.M.; Shaw, A.L.; Bortey, E.; Forbes, W.P.; et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N. Engl. J. Med.* **2011**, *364*, 22–32. [CrossRef] [PubMed]
76. Lembo, A.; Pimentel, M.; Rao, S.S.; Schoenfeld, P.; Cash, B.; Weinstock, L.B.; Paterson, C.; Bortey, E.; Forbes, W.P. Repeat Treatment With Rifaximin Is Safe and Effective in Patients With Diarrhea-Predominant Irritable Bowel Syndrome. *Gastroenterology* **2016**, *151*, 1113–1121. [CrossRef] [PubMed]
77. Dove, L.S.; Lembo, A.; Randall, C.W.; Fogel, R.; Andrae, D.; Davenport, J.M.; McIntyre, G.; Almenoff, J.S.; Covington, P.S. Eluxadoline benefits patients with irritable bowel syndrome with diarrhea in a phase 2 study. *Gastroenterology* **2013**, *145*, 329–338.e321. [CrossRef]

78. Lembo, A.J.; Lacy, B.E.; Zuckerman, M.J.; Schey, R.; Dove, L.S.; Andrae, D.A.; Davenport, J.M.; McIntyre, G.; Lopez, R.; Turner, L.; et al. Eluxadoline for Irritable Bowel Syndrome with Diarrhea. *N. Engl. J. Med.* **2016**, *374*, 242–253. [CrossRef]
79. Lacy, B.E.; Chey, W.D.; Cash, B.D.; Lembo, A.J.; Dove, L.S.; Covington, P.S. Eluxadoline Efficacy in IBS-D Patients Who Report Prior Loperamide Use. *Am. J. Gastroenterol.* **2017**, *112*, 924–932. [CrossRef]
80. Brenner, D.M.; Sayuk, G.S.; Gutman, C.R.; Jo, E.; Elmes, S.J.R.; Liu, L.W.C.; Cash, B.D. Efficacy and Safety of Eluxadoline in Patients With Irritable Bowel Syndrome With Diarrhea Who Report Inadequate Symptom Control With Loperamide: RELIEF Phase 4 Study. *Am. J. Gastroenterol.* **2019**, *114*, 1502–1511. [CrossRef]
81. Cangemi, D.J.; Lacy, B.E. Management of irritable bowel syndrome with diarrhea: A review of nonpharmacological and pharmacological interventions. *Ther. Adv. Gastroenterol.* **2019**, *12*, 1756284819878950. [CrossRef]
82. US Food and Drug Administration. *FDA Drug Safety Communication: FDA Warns about Increased Risk of Serious Pancreatitis with Irritable Bowel Drug Viberzi (Eluxadoline) in Patients without a Gallbladder*; Center for Drug Evaluation and Research: Beltsville, MD, USA, 2017.
83. Xie, C.; Tang, Y.; Wang, Y.; Yu, T.; Wang, Y.; Jiang, L.; Lin, L. Efficacy and Safety of Antidepressants for the Treatment of Irritable Bowel Syndrome: A Meta-Analysis. *PLoS ONE* **2015**, *10*, e0127815. [CrossRef]
84. Vahedi, H.; Merat, S.; Momtahen, S.; Kazzazi, A.S.; Ghaffari, N.; Olfati, G.; Malekzadeh, R. Clinical trial: The effect of amitriptyline in patients with diarrhoea-predominant irritable bowel syndrome. *Aliment. Pharmacol. Ther.* **2008**, *27*, 678–684. [CrossRef]
85. Lacy, B.E.; Nicandro, J.P.; Chuang, E.; Earnest, D.L. Alosetron use in clinical practice: Significant improvement in irritable bowel syndrome symptoms evaluated using the US Food and Drug Administration composite endpoint. *Ther. Adv. Gastroenterol.* **2018**, *11*, 1756284818771674. [CrossRef]
86. Tong, K.; Nicandro, J.P.; Shringarpure, R.; Chuang, E.; Chang, L. A 9-year evaluation of temporal trends in alosetron postmarketing safety under the risk management program. *Ther. Adv. Gastroenterol.* **2013**, *6*, 344–357. [CrossRef]
87. Camilleri, M.; Chey, W.Y.; Mayer, E.A.; Northcutt, A.R.; Heath, A.; Dukes, G.E.; McSorley, D.; Mangel, A.M. A randomized controlled clinical trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant irritable bowel syndrome. *Arch. Intern. Med.* **2001**, *161*, 1733–1740. [CrossRef]
88. Bharucha, A.E.; Wald, A. Chronic Constipation. *Mayo Clin. Proc.* **2019**, *94*, 2340–2357. [CrossRef] [PubMed]
89. Chapman, R.W.; Stanghellini, V.; Geraint, M.; Halphen, M. Randomized clinical trial: Macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. *Am J Gastroenterol* **2013**, *108*, 1508–1515. [CrossRef]
90. Talley, N.J. Pharmacologic therapy for the irritable bowel syndrome. *Am. J. Gastroenterol.* **2003**, *98*, 750–758. [CrossRef]
91. Wilson, N.; Schey, R. Lubiprostone in constipation: Clinical evidence and place in therapy. *Ther. Adv. Chronic Dis.* **2015**, *6*, 40–50. [CrossRef] [PubMed]
92. Bonetto, S.; Fagoonee, S.; Battaglia, E.; Grassini, M.; Saracco, G.M.; Pellicano, R. Recent advances in the treatment of irritable bowel syndrome. *Pol. Arch. Intern. Med.* **2021**, *131*, 709–715. [CrossRef]
93. Johanson, J.F.; Morton, D.; Geenen, J.; Ueno, R. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. *Am. J. Gastroenterol.* **2008**, *103*, 170–177. [CrossRef] [PubMed]
94. Atluri, D.K.; Chandar, A.K.; Bharucha, A.E.; Falck-Ytter, Y. Effect of linaclotide in irritable bowel syndrome with constipation (IBS-C): A systematic review and meta-analysis. *Neurogastroenterol. Motil.* **2014**, *26*, 499–509. [CrossRef]
95. Rao, S.S.; Quigley, E.M.; Shiff, S.J.; Lavins, B.J.; Kurtz, C.B.; MacDougall, J.E.; Currie, M.G.; Johnston, J.M. Effect of linaclotide on severe abdominal symptoms in patients with irritable bowel syndrome with constipation. *Clin. Gastroenterol. Hepatol.* **2014**, *12*, 616–623. [CrossRef] [PubMed]
96. Johnston, J.M.; Kurtz, C.B.; Macdougall, J.E.; Lavins, B.J.; Currie, M.G.; Fitch, D.A.; O'Dea, C.; Baird, M.; Lembo, A.J. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome with constipation. *Gastroenterology* **2010**, *139*, 1877–1886.e2. [CrossRef]
97. Brenner, D.M.; Fogel, R.; Dorn, S.D.; Krause, R.; Eng, P.; Kirshoff, R.; Nguyen, A.; Crozier, R.A.; Magnus, L.; Griffin, P.H. Efficacy, safety, and tolerability of plecanatide in patients with irritable bowel syndrome with constipation: Results of two phase 3 randomized clinical trials. *Am. J. Gastroenterol.* **2018**, *113*, 735–745. [CrossRef]
98. Herekar, A.; Shimoga, D.; Jehangir, A.; Shahsavari, D.; Yan, Y.; Karunaratne, T.B.; Sharma, A. Tenapanor in the Treatment of Irritable Bowel Syndrome with Constipation: Discovery, Efficacy, and Role in Management. *Clin. Exp. Gastroenterol.* **2023**, *16*, 79–85. [CrossRef] [PubMed]
99. Chey, W.D.; Lembo, A.J.; Yang, Y.; Rosenbaum, D.P. Efficacy of Tenapanor in Treating Patients With Irritable Bowel Syndrome With Constipation: A 26-Week, Placebo-Controlled Phase 3 Trial (T3MPO-2). *Am. J. Gastroenterol.* **2021**, *116*, 1294–1303. [CrossRef]
100. Wechsler, E.V.; Shah, E.D. Diarrhea-Predominant and Constipation-Predominant Irritable Bowel Syndrome: Current Prescription Drug Treatment Options. *Drugs* **2021**, *81*, 1953–1968. [CrossRef] [PubMed]
101. Sayuk, G.S.; Tack, J. Tegaserod: What's Old Is New Again. *Clin. Gastroenterol. Hepatol.* **2022**, *20*, 2175–2184.e19. [CrossRef]
102. Tack, J.; Camilleri, M.; Chang, L.; Chey, W.D.; Galligan, J.J.; Lacy, B.E.; Muller-Lissner, S.; Quigley, E.M.; Schuurkes, J.; De Maeyer, J.H.; et al. Systematic review: Cardiovascular safety profile of 5-HT(4) agonists developed for gastrointestinal disorders. *Aliment. Pharmacol. Ther.* **2012**, *35*, 745–767. [CrossRef]

103. Wright, K.; Rooney, N.; Feeney, M.; Tate, J.; Robertson, D.; Welham, M.; Ward, S. Differential expression of cannabinoid receptors in the human colon: Cannabinoids promote epithelial wound healing. *Gastroenterology* **2005**, *129*, 437–453. [CrossRef]
104. Dothel, G.; Chang, L.; Shih, W.; Barbaro, M.R.; Cremon, C.; Stanghellini, V.; De Ponti, F.; Mayer, E.A.; Barbara, G.; Sternini, C. micro-opioid receptor, beta-endorphin, and cannabinoid receptor-2 are increased in the colonic mucosa of irritable bowel syndrome patients. *Neurogastroenterol. Motil.* **2019**, *31*, e13688. [CrossRef]
105. Kikuchi, A.; Ohashi, K.; Sugie, Y.; Sugimoto, H.; Omura, H. Pharmacological evaluation of a novel cannabinoid 2 (CB2) ligand, PF-03550096, in vitro and in vivo by using a rat model of visceral hypersensitivity. *J. Pharmacol. Sci.* **2008**, *106*, 219–224. [CrossRef] [PubMed]
106. Chang, L.; Cash, B.D.; Lembo, A.; Kunkel, D.C.; English, B.A.; Lindstrom, B.; Gu, G.; Skare, S.; Gilder, K.; Turner, S.; 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. [CrossRef] [PubMed]
107. Leventer, S.M.; Raudibaugh, K.; Frissora, C.L.; Kassem, N.; Keogh, J.C.; Phillips, J.; Mangel, A.W. Clinical trial: Dextofisopam in the treatment of patients with diarrhoea-predominant or alternating irritable bowel syndrome. *Aliment. Pharmacol. Ther.* **2008**, *27*, 197–206. [CrossRef] [PubMed]
108. Quigley, E.M.M.; Markinson, L.; Stevenson, A.; Treasure, F.P.; Lacy, B.E. Randomised clinical trial: Efficacy and safety of the live biotherapeutic product MRx1234 in patients with irritable bowel syndrome. *Aliment. Pharmacol. Ther.* **2023**, *57*, 81–93. [CrossRef]