IRRITABLE BOWEL SYNDROME (IBS)

CHI Formulary Indication Review

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INDICATION UPDATE

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ADDENDUM to the CHI Original Irritable Bowel Syndrome Clinical Guidance- Issued March 2020

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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Abbreviations

ACG	American College of Gastroenterology
AGA	American Gastroenterological Association
AIGO	Italian Association of Hospital Gastroenterologists and Endoscopists
CHI	Council of Health Insurance
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDr	Functional Diarrhea
FMT	Fecal Microbiota Transplantation
FODMAP	Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
IBS	Irritable Bowel Syndrome
IBS-C	Irritable Bowel Syndrome with Constipation
IBS-D	Irritable Bowel Syndrome with Diarrhea
OTC	Over the Counter
PA	Prior Authorization
PEG	Polyethylene Glycol
RDN	Registered Dietitian Nutritionist
SFDA	Saudi Food and Drug Authority
SIED	Digestive Endoscopy
SIGE	Gastroenterology and Endoscopy
SIGENP	Gastroenterology, Hepatology and Pediatric Nutrition
SIMG	General Medicine
SINGEM	Neurogastroenterology and Motility
SIP	Pediatrics
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant
TIA	Transient Ischemic Attack

Executive Summary

Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder characterized by recurrent abdominal pain or discomfort associated with changes in bowel habits. These changes may include diarrhea, constipation, or a combination of both. The pain or discomfort is often relieved with bowel movements[1].

The signs and symptoms of IBS include abdominal pain/discomfort, changes in bowel habits (diarrhea, constipation, or both), bloating, gas or flatulence and fatigue[1].

IBS can be classified into four main types according to Rome IV criteria:

- **IBS with Diarrhea (IBS-D):** characterized by frequent episodes of diarrhea, loose or watery stools, and urgency to have bowel movements. People with IBS-D may experience abdominal pain and discomfort, often relieved after a bowel movement. Bloating and gas can also be present.
- **IBS with Constipation (IBS-C):** characterized by constipation and difficulties with bowel movements. Individuals with IBS-C may have infrequent bowel movements, hard or lumpy stools, and a feeling of incomplete evacuation. Abdominal discomfort and bloating may also be present.
- **Mixed IBS (IBS-M):** Mixed-type IBS involves a combination of both diarrhea and constipation symptoms. Individuals may alternate between episodes of diarrhea and constipation. Abdominal pain, bloating, and gas can occur in this subtype as well[2].
- **IBS undifferentiated (IBS-U):** Symptoms vary with no regular pattern.

Complications associated with IBS include dietary restrictions, psychological distress, impaired work, disrupted sleep, and exacerbation of other health conditions, such as hemorrhoids, gastroesophageal reflux disease (GERD), or pelvic floor dysfunction[1].

IBS is a chronic and debilitating functional gastrointestinal disorder that affects 10%-23% of the population across the world with women and adults who are less than 50 years old being more vulnerable to developing IBS. Due to the recurrent and enduring symptoms associated with IBS, it leads to a reduction in quality of life, substantial absenteeism, and a significant socioeconomic burden[3].

A study conducted in 2020 on the general population in central Saudi Arabia revealed an overall IBS prevalence of 30.5% using Rome III criteria[4]. Another study conducted in 2021 in Jazan according to the Rome IV criteria found that the overall prevalence of IBS among the Jazan general population in Saudi Arabia was 16%[5].

IBS causes a considerable burden on healthcare systems globally. As emphasized in a recent review paper, the direct medical expenses associated with IBS in the United States, not including expenses for prescription and over-the-counter medications,

are estimated to range from $1.5 billion to $10 billion annually. This substantial financial burden is exacerbated by excessive use of healthcare resources, frequent and sometimes unnecessary testing, and significant regional disparities in testing and treatment, all of which contribute to substantial costs, both direct and indirect[6].

Drug therapy is an integral component for the management of IBS.

The objectives of treatment for irritable bowel syndrome encompass relief of symptom, improve quality of life and adopting an individualized approach for each patient. Depending on the predominant symptoms (diarrhea, constipation, pain), different medications may be prescribed to patients. These can include antispasmodics, laxatives, anti-diarrheal agents, medications that affect gut motility, tricyclic antidepressants, selective serotonin reuptake inhibitors and rifaximin. This is why having an individualized approach is essential. However, due to the increased prevalence of IBS worldwide and the global impact it has on patients; alternative agents and strategies are needed in both the short- and long-term treatment of irritable bowel syndrome[7].

CHI issued irritable bowel syndrome (IBS) clinical guidance after thorough review of renowned international and national clinical guidelines in March 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Irritable Bowel Syndrome (IBS) clinical guidance and seeks to offer guidance for the effective management of IBS. It provides an **update on the irritable bowel syndrome (IBS) Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being **new guidelines added to the report** such as AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome With Diarrhea **(2022)**, AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome With Constipation **(2022)**, ACG Clinical Guideline: Management of Irritable Bowel Syndrome **(2020)**, AGA Clinical Practice Update on the Role of Diet in Irritable Bowel Syndrome: Expert Review **(2022)**, Functional bowel disorders with diarrhea: Clinical guidelines of the United European Gastroenterology and European Society for Neurogastroenterology and Motility **(2022),** British Society of Gastroenterology guidelines on the management of irritable bowel syndrome **(2021)**, Italian guidelines for the management of irritable bowel syndrome Joint Consensus from the Italian Societies of: Gastroenterology and Endoscopy (SIGE), Neurogastroenterology and Motility (SINGEM), Hospital Gastroenterologists and Endoscopists (AIGO), Digestive Endoscopy (SIED), General Medicine (SIMG), Gastroenterology, Hepatology and Pediatric Nutrition (SIGENP) and Pediatrics (SIP) **(2023)**, Belgian consensus on

irritable bowel syndrome **(2022)**, Guidelines on the management of irritable bowel syndrome Gastroenterology Review **(2018)** and The Japanese Society of Gastroenterology Evidence-based clinical practice guidelines for irritable bowel syndrome **(2021).**

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is important to note that there has been **withdrawal** of drugs:

- Amitriptyline hydrochloride
- Trimebutine
- Vitamins, folic acid, pantothenic acid, calcium, lactic ferments (lactobacillus acidophilus & sporogenes, Bifidobacterium bifidum, longum & infantis)

Moreover, there has been **a newly approved drug** for the treatment of IBS: **Tenapanor** which was FDA approved in 2019 but not SFDA registered. **Tegaserod,** an old medication; was approved by the FDA in 2002 but is not SFDA registered.

Additionally, there have been **updates** regarding previously mentioned drugs in terms of drug information and prescribing edits since March 2020. Imipramine hydrochloride does not need PA as a prescribing edit. Loperamide has an AGE prescribing edit: it is contraindicated in children < 2 years old. However, it does not require a MD as a prescribing edit as it is available OTC. Mebeverine hydrochloride has an AGE prescribing edit: it is not recommended in children < 18 years old. Paroxetine has an AGE prescribing edit: children < 18 years old should not normally take it.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the irritable bowel syndrome (IBS) therapeutic management.

Below is a table summarizing the major changes based on the different irritable bowel syndrome (IBS) guidelines used to issue this report:

Table 1. General Recommendations for the Management of Irritable Bowel Syndrome

Management of Irritable Bowel Syndrome (IBS)		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
Consider dietary changes, including traditional dietary advice, and potentially a limited trial	Conditional recommendation; very low quality of evidence[6]	ACG (2021)[6] British Society of Gastroenterology (2021)[8]

of low FODMAP diet, but under the guidance of a healthcare professional	Strong recommendation; weak quality of evidence[8,9] Grade B[10] Weak recommendation, moderate quality of evidence[11]	& SIGE/SINGEM/AIGO/SIED/ SIMG/SIGENP/SIP (2023)[9] Belgian consensus (2022)[10] Japanese Society of Gastroenterology (2020)[11]
Soluble fiber can be effective in managing IBS symptoms, while insoluble fiber should be avoided because they can exacerbate symptoms. Increasing dietary fiber for people with irritable bowel syndrome (IBS) can be beneficial for many, but it should be done gradually and with caution as it can potentially worsen IBS symptoms in some individuals	Strong recommendation; moderate quality of evidence[6,7,11] Strong recommendation, high quality of evidence [11]	ACG (2021)[6] & Przeglad Gastroenterologiczny (2018)[12] Japanese Society of Gastroenterology (2020)[11]
A gluten-free diet is generally not recommended for IBS	Weak recommendation; very low quality of evidence[6,7] Not graded[13] Grade C[10] Strong recommendation; low[9] Strong recommendation, low level of evidence[14]	ACG (2021)[6] & Gastroenterology Review (2021)[7] AGA (2022)[13] Belgian consensus[10] SIGE/SINGEM/AIGO/SIED/ SIMG/SIGENP/SIP[9] United European Gastroenterology and European Society for Neurogastroenterology and Motility[14]
Engaging in regular physical activity and considering stress	Weak recommendation, very low quality of evidence[7]	Przeglad Gastroenterologiczny (2018)[12]

management techniques is essential for symptom management of IBS	[13]Strong recommendation; weak quality of evidence[8]	British Society of Gastroenterology (2021)[8]
For IBS-D treatment: Eluxadoline may be used, but is contraindicated in certain cases such as: in patients without a gallbladder or those who drink more than 3 alcoholic beverages per day	Conditional recommendation; moderate evidence[15] Weak recommendation; moderate quality of evidence[8] Quality of evidence: moderate[7] Strong recommendation, high level of evidence[14]	AGA (2022)[15] British Society of Gastroenterology (2021)[8] Przeglad Gastroenterologiczny (2018)[12] United European Gastroenterology and European Society for Neurogastroenterology and Motility[14]
For IBS-D treatment: Rifaximin can be considered, and retreatment may be necessary for recurrent symptoms	Conditional recommendation, moderate evidence[15] Strong recommendation; moderate quality of evidence[6] Weak recommendation, quality of evidence: moderate quality of evidence[8] Strong recommendation; high quality of evidence[7] Strong recommendation, high level of evidence[14]	AGA (2022)[15] ACG (2021)[6] British Society of Gastroenterology (2021)[8] Przeglad Gastroenterologiczny (2018)[12] United European Gastroenterology and European Society for Neurogastroenterology and Motility[14]
For IBS-D treatment: Alosetron is suggested for symptom relief **to relieve global IBS-D symptoms in women with severe symptoms who have failed conventional therapy**. It should also be under specific risk management program.	Conditional recommendation, moderate evidence[15] Conditional recommendation; low quality of evidence[6] Quality of evidence: low[7]	AGA (2022)[15] ACG (2021)[6] Przeglad Gastroenterologiczny (2018)[12]

For IBS-D treatment: Loperamide may be considered	Conditional recommendation; very low evidence[15] Strong recommendation; very low quality of evidence[8] Grade B[10] Weak recommendation, very low quality of evidence[7] Strong recommendation, low level of evidence[14]	AGA (2022)[15] British Society of Gastroenterology (2021)[8] Belgian consensus[10] Przeglad Gastroenterologiczny (2018)[12] United European Gastroenterology and European Society for Neurogastroenterology and Motility[14]
Recommend against the use of mesalazine in patients with IBS-D or FDr	Strong recommendation, moderate level of evidence[14]	United European Gastroenterology and European Society for Neurogastroenterology and Motility[14]
For IBS-C treatment: Linaclotide is recommended in severe cases and upon failure of first line options	Quality of evidence: high[7] Strong recommendation, high evidence[8,16] Grade C[10]	Przeglad Gastroenterologiczny (2018)[12] British Society of Gastroenterology (2021)[8] AGA (2022)[16] Belgian consensus[10]
For IBS-C treatment: Lubiprostone; acts as a chloride channel activator, serves as an effective secondary treatment option for constipation-predominant IBS in clinical settings. Unlike some other options, it has a lower likelihood of causing diarrhea. However, it's important to advise patients about the relatively frequent	Conditional recommendation, moderate evidence[16] Strong recommendation; moderate quality of evidence[8] Quality of evidence: moderate[12]	AGA (2022)[16] British Society of Gastroenterology (2021)[8] Przeglad Gastroenterologiczny (2018)[12]

occurrence of nausea as a side effect		
For IBS-C treatment: Plecanatide; functions as a guanylate cyclase-C agonist, proves to be an effective secondary treatment choice for constipation-predominant IBS in clinical settings. However, it's important to note that diarrhea is a frequent side effect, akin to linaclotide or tenapanor. While it has gained approval for treating IBS with constipation in the United States, its approval for the same indication is still pending in several other countries. can be considered[16].	Conditional recommendation, moderate evidence[16] Strong recommendation, high quality of evidence[8] Quality of evidence: moderate[12]	AGA (2022)[16] British Society of Gastroenterology (2021)[8] Przeglad Gastroenterologiczny (2018)[12]
For IBS-C treatment: Tegaserod is an option, primarily for women under 65 without a history of cardiovascular ischemic events, such as myocardial infarction, stroke, TIA, or angina	Conditional recommendation, moderate evidence[16] Strong/conditional recommendation; low quality of evidence[6] Strong recommendation, moderate quality of evidence[8]	AGA (2022)[16] ACG (2021)[6] British Society of Gastroenterology (2021)[8]
For IBS-C treatment: Polyethylene glycol (PEG) laxatives may be used	Weak recommendation; very low quality of evidence[8] Conditional recommendation, very low quality of evidence[9] Weak recommendation, low quality of evidence[12]	British Society of Gastroenterology (2021)[8] SIGE/SINGEM/AIGO/SIED/ SIMG/SIGENP/SIP[9] Przeglad Gastroenterologiczny (2018)[12]

For IBS-C treatment: Prucalopride is recommended for severe constipation	Grade A[10]	Belgian consensus[10]
For IBS-C treatment: Osmotic laxatives may be considered	Grade C[10] Weak recommendation, evidence level C[11]	Belgian consensus[10] Japanese Society of Gastroenterology (2020)[11]
For IBS-C treatment: Tenapanor; an inhibitor of the sodium-hydrogen exchange, is a potent secondary treatment option for constipation-predominant IBS in a clinical setting. It's worth noting that diarrhea remains a commonly observed side effect. Although it has received approval for treating IBS with constipation in the United States, its accessibility for this specific indication is limited in numerous countries	Conditional recommendation, moderate evidence[16] Strong recommendation, high quality of evidence[8]	AGA (2022)[16] British Society of Gastroenterology (2021)[8]
In general, medications for management of global IBS symptoms include: Antispasmodics may be considered but with limited evidence.	Conditional recommendation, low evidence[7,9,15,16] Weak recommendation, very low quality of evidence[8]	Gastroenterology Review (2021)[7] SIGE/SINGEM/AIGO/SIED/ SIMG/SIGENP/SIP[9] AGA (2022)[15] AGA (2022)[16] British Society of Gastroenterology (2021)[8]
Recommend against the use of antispasmodics for the treatment of global IBS symptoms.	Conditional recommendation; low quality of evidence[6]	ACG (2021)[6]

Recommend the utilization of antispasmodic agents in patients with IBS-D but note the absence of data for FDr.	Weak recommendation, low level of evidence[14]	United European Gastroenterology and European Society for Neurogastroenterology and Motility[14]
Tricyclic antidepressants (TCAs) can be effective.	Strong recommendation; moderate quality of evidence[6,8,9] Grade B[10] Strong recommendation, high quality of evidence[12] Weak recommendation, high quality of evidence[11]	ACG (2021)[6] British Society of Gastroenterology (2021)[8] SIGE/SINGEM/AIGO/SIED/ SIMG/SIGENP/SIP[9] Belgian consensus[10] Przeglad Gastroenterologiczny (2018)[12] Japanese Society of Gastroenterology (2020)[11]
Selective serotonin reuptake inhibitors (SSRIs) may be used with caution but there is no consensus among guidelines; some suggest its use while others do not recommend it	Weak recommendation, low quality of evidence[8,12] Conditional recommendation; low quality of evidence[6,9] Grade B[10] Weak recommendation, high quality of evidence[11] Conditional recommendation, very low quality of evidence[14]	Przeglad Gastroenterologiczny (2018)[12] British Society of Gastroenterology (2021)[8] ACG (2021)[6] SIGE/SINGEM/AIGO/SIED/ SIMG/SIGENP/SIP[9] Belgian consensus[10] Japanese Society of Gastroenterology (2020)[11] United European Gastroenterology and European Society for Neurogastroenterology and Motility[14]
Recommend the use of 5-HT3 antagonists (alosetron, ondansetron, ramosetron) in treating patients with IBS-D to improve IBS symptoms,	Strong recommendation, moderate level of evidence[14]	United European Gastroenterology and European Society for Neurogastroenterology and Motility[14]

but highlight the lack of evidence for FDr		
Suggest against probiotics for the treatment of global IBS symptoms	Conditional recommendation; very low quality of evidence[6]	ACG (2021)[6]
Probiotics may be considered for a maximum duration of 12 weeks, but specific strains should be chosen	Weak recommendation, very low quality of evidence[8, 12] Conditional recommendation, low quality of evidence[9] Grade C[10] Strong recommendation, high quality of evidence [11]	Przeglad Gastroenterologiczny (2018)[12] British Society of Gastroenterology (2021)[8] SIGE/SINGEM/AIGO/SIED/ SIMG/SIGENP/SIP[9] Belgian consensus[10] Japanese Society of Gastroenterology (2020)[11]
Peppermint oil might offer potential effectiveness in symptom relief	Conditional recommendation; low quality of evidence[6] Weak recommendation, very low quality of evidence[8] Strong recommendation, moderate quality of evidence[12] Weak recommendation, high quality of evidence [11]	ACG (2021)[6] British Society of Gastroenterology (2021)[8] Przeglad Gastroenterologiczny (2018)[12] Japanese Society of Gastroenterology (2020)[11]
Fecal microbiota transplantation (FMT) is not recommended for IBS	Strong recommendation, low quality of evidence[9] Weak recommendation, very low quality of evidence[12] Strong recommendation; very low quality of evidence[6] Grade B[10] No grading[11] Strong recommendation, low level of evidence[14]	SIGE/SINGEM/AIGO/SIED/ SIMG/SIGENP/SIP[9] Przeglad Gastroenterologiczny (2018)[12] ACG (2021)[6] Belgian consensus[10] Japanese Society of Gastroenterology (2020)[11] United European Gastroenterology and European Society for

		Neurogastroenterology and Motility[14]
Simethicone in monotherapy is not effective in IBS	Grade D[10]	Belgian consensus[10]
Kampo medicine (traditional Japanese medicine) is effective in treating IBS. Kampo agents are recommended for IBS	Weak recommendation, evidence level C[11]	Japanese Society of Gastroenterology (2020)[11]

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **irritable bowel syndrome (IBS) clinical and therapeutic management.**

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts; one part includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Irritable Bowel Syndrome (IBS) report, and the other part includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

The following segment contains the updated versions of the guidelines mentioned in the March 2020 CHI Irritable Bowel Syndrome (IBS) Report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
1.1 American Gastroenterological Association Institute Guideline on the Use of Pharmacological Therapies in the Treatment of Irritable Bowel Syndrome **(2019 Update)**	N/A*
1.2 American College of Gastroenterology Monograph on Management of Irritable Bowel Syndrome **(2018)**	N/A*
1.3 Canadian Association of Gastroenterology Clinical Practice Guideline for the Management of Irritable Bowel Syndrome **(2019)**	N/A*
1.4 National Institute for Health Care and Excellence [NICE] Recommendations for Medical Management of Irritable Bowel Syndrome **(2017)**	N/A*

**N/A: not available (no new updates for those guidelines)*

1.2 Additional Guidelines

This section includes the added guidelines to the previous CHI Irritable Bowel Syndrome (IBS) report, along with their recommendations.

Table 3. List of Additional Guidelines

Additional Guidelines
AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome with Diarrhea **(2022)**
AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome with Constipation **(2022)**
ACG Clinical Guideline: Management of Irritable Bowel Syndrome **(2020)**
AGA Clinical Practice Update on the Role of Diet in Irritable Bowel Syndrome: Expert Review **(2022)**
Functional Bowel Disorders with Diarrhea: Clinical Guidelines of the **United European Gastroenterology** and **European Society for Neurogastroenterology and Motility** (**2022**)
British Society of Gastroenterology Guidelines on the Management of Irritable Bowel Syndrome **(2021)**
Italian Guidelines for the Management of Irritable Bowel Syndrome Joint Consensus from the Italian Societies of: Gastroenterology and Endoscopy (SIGE), Neurogastroenterology and Motility (SINGEM), Hospital Gastroenterologists and Endoscopists (AIGO), Digestive Endoscopy (SIED), General Medicine (SIMG), Gastroenterology, Hepatology and Pediatric Nutrition (SIGENP) and Pediatrics (SIP) **(2023)**
Belgian Consensus on Irritable Bowel Syndrome **(2022)**
Guidelines on the Management of Irritable Bowel Syndrome Gastroenterology Review **(2018)**
The **Japanese Society of Gastroenterology** Evidence-Based Clinical Practice Guidelines for Irritable Bowel Syndrome **(2020)**

1.2.1 AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome with Diarrhea (2022)

The American Gastroenterological Association (AGA) published its 2022 guidelines[15] for the management of IBS, and have opted for the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to assess evidence and make recommendations.

Table 4. AGA Grading of Recommendations, Assessment, Development and Evaluation Framework

Implications	Strong recommendations	Conditional recommendations
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients consistent with his or her values and preferences. Use shared decision making. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values, and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations.	Policy making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.

NOTE. Strong recommendations are indicated by statements that lead with "we recommend" and conditional recommendations are indicated by statements that lead with "we suggest."

The AGA has issued the recommendations below[15]:

- In patients with IBS-D, use eluxadoline. To note that eluxadoline is contraindicated in patients without a gallbladder or those who drink more than 3 alcoholic beverages per day (conditional recommendation, moderate evidence).
- In patients with IBS-D, it is suggested to use rifaximin (conditional recommendation, moderate evidence).

- In patients with IBS-D with initial response to rifaximin who develop recurrent symptoms, it is suggested to retreat with rifaximin (conditional recommendation, moderate evidence).
- In patients with IBS-D, it is suggested to use alosetron (conditional recommendation, moderate evidence).
- In patients with IBS-D, it is suggested to use loperamide (conditional recommendation, very low evidence).
- In patients with IBS, it is suggested to use TCAs (conditional recommendation, low evidence).
- In patients with IBS, advise not to use SSRIs (conditional recommendation, low evidence).
- In patients with IBS, the AGA suggests using antispasmodics (conditional recommendation, low evidence).

1.2.2 AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome with Constipation (2022)

The 2022 AGA guidelines[16] for IBS-C follows the GRADE framework detailed in table 4 above.

The main recommendations are stated below[16]:

- In patients with IBS-C, it is suggested to use tenapanor (conditional recommendation, moderate evidence).
- In patients with IBS-C, it is suggested to use plecanatide (conditional recommendation, moderate evidence).
- In patients with IBS-C, it is **recommended** to use linaclotide (strong recommendation, high evidence).
- In patients with IBS-C, it is suggested to use tegaserod. To note that Tegaserod was reapproved for women under the age of 65 years without a history of cardiovascular ischemic events (such as myocardial infarction, stroke, TIA, or angina) (conditional recommendation, moderate evidence).
- In patients with IBS-C, it is suggested to use lubiprostone (conditional recommendation, moderate evidence).
- In patients with IBS-C, it is suggested to use PEG laxatives (conditional recommendation, low evidence).
- In patients with IBS, it is suggested to use TCAs (conditional recommendation, low evidence).

- In patients with IBS, advise not to use SSRIs (conditional recommendation, low evidence).
- In patients with IBS, it is suggested to use antispasmodics (conditional recommendation, low evidence).

1.2.3 ACG Clinical Guideline: Management of Irritable Bowel Syndrome (2020)

The American College of Gastroenterology (ACG) published its clinical guidelines for the management of IBS in 2020, and have opted for grading scheme detailed in table 5[6]:

Table 5. Grading the Certainty of Evidence and Strength of Recommendations of ACG Clinical Guidelines

Recommendation	Quality of evidence
Strong: The strength of recommendation is given as strong if most patients should receive the recommended course of action	**High**—the estimate of effect is unlikely to change with new data
Conditional: The strength of recommendation is given as conditional if many patients should have this recommended course of action, but different choices may be appropriate for some patients	**Moderate**; **low**; **very low**—estimate of effect is very uncertain

The ACG has issued the recommendations below[6]:

- Recommend a limited trial of a low FODMAP diet in patients with IBS to improve global IBS symptoms (Conditional recommendation; very low quality of evidence).
- Suggest that soluble, but not insoluble, fiber be used to treat global IBS symptoms (Strong recommendation; moderate quality of evidence).
- Recommend against the use of antispasmodics for the treatment of global IBS symptoms (Conditional recommendation; low quality of evidence).
- Suggest the use of peppermint to provide relief of global IBS symptoms (Conditional recommendation; low quality of evidence).
- Suggest against probiotics for the treatment of global IBS symptoms (Conditional recommendation; very low quality of evidence).

- Suggest against PEG products to relieve global IBS symptoms in those with IBS-C (Conditional recommendation; low quality of evidence).
- Recommend the use of chloride channel activators to treat global IBS-C symptoms (Strong recommendations; moderate quality of evidence).
- Recommend the use of guanylate cyclase activators to treat global IBS-C symptoms (Strong recommendation; high quality of evidence).
- Suggest that the 5-HT4 agonist tegaserod be used to treat IBS-C symptoms in women younger than 65 years with ≤ 1 cardiovascular risk factors who have not adequately responded to secretagogues (Strong/conditional recommendation; low quality of evidence)
- Do not suggest the use of bile acid sequestrants to treat global IBS-D symptoms (Conditional recommendation; very low quality of evidence).
- Recommend the use of rifaximin to treat global IBS-D symptoms (Strong recommendation; moderate quality of evidence).
- Recommend that alosetron be used to relieve global IBS-D symptoms in women with severe symptoms who have failed conventional therapy (Conditional recommendation; low quality of evidence).
- Suggest that mixed opioid agonists/antagonists be used to treat global IBS-D symptoms (Conditional recommendation; moderate quality of evidence).
- Recommend that tricyclic antidepressants be used to treat global symptoms of IBS (Strong recommendation; moderate quality of evidence).
- Suggest that gut-directed psychotherapies be used to treat global IBS symptoms (Conditional recommendations; very low quality of evidence).
- Based on the existing evidence, we advise not to consider fecal transplant as a treatment option for overall IBS symptoms (Strong recommendation; very low quality of evidence).

1.2.4 AGA Clinical Practice Update on the Role of Diet in Irritable Bowel Syndrome: Expert Review (2022)

The AGA has issued the recommendations below[13]:

- Dietary advice is ideally prescribed to patients with IBS who have insight into their meal-related gastrointestinal symptoms and are motivated to make the necessary changes. To optimize the quality of teaching and clinical response, referral to a registered dietitian nutritionist (RDN) should be made to patients who are willing to collaborate with a RDN and patients who are not able to implement beneficial dietary changes on their own. If a gastrointestinal RDN

is not available, other resources can assist with implementation of diet interventions.

- Patients with IBS who are poor candidates for restrictive diet interventions include those consuming few culprit foods, those at risk for malnutrition, those who are food insecure, and those with an eating disorder or uncontrolled psychiatric disorder. Routine screening for disordered eating or eating disorders by careful dietary history is critical because they are common and often overlooked in gastrointestinal conditions.
- Specific diet interventions should be attempted for a predetermined length of time. If there is no clinical response, the diet intervention should be abandoned for another treatment alternative, for example, a different diet, medication, or other form of therapy.
- In preparation for a visit with a RDN, patients should provide dietary information that will assist in developing an individualized nutrition care plan.
- Soluble fiber is efficacious in treating global symptoms of IBS.
- The low-FODMAP diet is currently the most evidence- based diet intervention for IBS. Healthy eating advice as described by the National Institute of Health and Care Excellence Guidelines, among others, also offers benefit to a subset of patients with IBS.
- The low-FODMAP diet consists of the following 3 phases:
    1. restriction (lasting no more than 4–6 weeks)
    2. reintroduction of FODMAP foods
    3. personalization based on results from reintroduction.
- Although observational studies found that most patients with IBS improve with a gluten-free diet, randomized controlled trials have yielded mixed results.
- There is limited data showing that selected biomarkers can predict response to diet interventions in patients with IBS, but there is insufficient evidence to support their routine use in clinical practice.

1.2.5 Functional Bowel Disorders with Diarrhea: Clinical Guidelines of the United European Gastroenterology and European Society for Neurogastroenterology and Motility (2022)

The United European Gastroenterology and European Society for Neurogastroenterology and Motility[14] have opted for the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system:

Table 6. Grading the Certainty of Evidence and Strength of Recommendations Using the GRADE Approach

Strength of recommendation	
Strong	Benefits clearly outweigh risks and burden or vice versa. Usually stated as: **"we recommend"**
Conditional	Benefits probably outweigh risks and burden, or vice versa, but there is appreciable uncertainty.
Weak	Benefits closely balanced with risks and burden. Usually stated as: **"we suggest"**
Evidence level (quality of evidence)	
High	One or more well-designed and well-executed randomized controlled trials (RCTs) that yield consistent and directly applicable results. This level also means that further research is very unlikely to change our confidence in the estimate of effect.
Moderate	RCTs with important limitations (i.e., biased assessment of the treatment effect, large loss to follow-up, lack of blinding, unexplained heterogeneity), indirect evidence originating from similar (but not identical) populations of interest, and RCTs with a very small number of participants or observed events. In addition, evidence from well-designed controlled trials without randomization, from well-designed cohort or case-control analytic studies, and from multiple time series with or without intervention is in this category. This level also means that further research will probably have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Observational studies would typically be rated as low quality because of the risk for bias. This level also means that further research is very likely to have an important impact on our confidence in the estimate of effect and will probably change the estimate.
Very low	Evidence is conflicting, of poor quality, or lacking, and hence the balance of benefits and harms cannot be determined. Any estimate of effect is very uncertain as evidence is either unavailable or does not permit a conclusion.

The United European Gastroenterology and European Society for Neurogastroenterology and Motility has issued the recommendations below[14]:

- Recommend the utilization of antispasmodic agents in patients with IBS-D, but note the absence of data for FDr (Weak recommendation, low level of evidence).
- Recommend the use of loperamide in patients with IBS-D or FDr (Strong recommendation, low level of evidence).
- Recommend the utilization of rifaximin in patients with IBS-D, acknowledging that the therapeutic gain over placebo may be limited. Limited evidence supports the efficacy of rifaximin in the treatment of FDr (Strong recommendation, high level of evidence).
- Recommend the use of probiotics that may enhance overall symptoms and alleviate diarrhea in some patients with IBS-D, but highlight the lack of evidence for FDr (Conditional recommendation, low level of evidence).
- Recommend against the use of mesalazine in patients with IBS-D or FDr (Strong recommendation, moderate level of evidence).
- Recommend the use of bile acid sequestrants in patients with confirmed bile acid diarrhea. If testing is unavailable, consider a trial of a bile acid sequestrant in patients with persistent unexplained chronic diarrhea (Moderate recommendation, moderate level of evidence).
- Recommend the short-term usefulness of a low FODMAPs diet in patients with IBS-D when other measures have failed but emphasize the absence of evidence for FDr (Strong recommendation, low level of evidence).
- Recommend against a gluten-free diet for patients with IBS-D, with no evidence supporting FDr (Strong recommendation, low level of evidence).
- Recommend gut-directed psychological therapies as an alternative treatment in patients with IBS-D but stress the lack of evidence for FDr (Strong recommendation, low level of evidence).
- Recommend against the use of fecal microbiota transplantation in patients with IBS-D or FDr (Strong recommendation, low level of evidence).
- Recommend the use of eluxadoline for treating patients with IBS-D, with no evidence supporting FDr (Strong recommendation, high level of evidence).
- Recommend the use of TCAs for treating patients with IBS-D, despite the absence of evidence for FDr (Consensus).
- Recommend against the use of SSRIs for treating patients with IBS-D or FDr (Conditional recommendation, very low quality of evidence).
- Recommend the use of 5-HT3 antagonists (alosetron, ondansetron, ramosetron) in treating patients with IBS-D to improve IBS symptoms but

highlight the lack of evidence for FDr (Strong recommendation, moderate level of evidence).

1.2.6 British Society of Gastroenterology Guidelines on the Management of Irritable Bowel Syndrome (2021)

The 2022 British Society of Gastroenterology guidelines[8] have opted for the Grading of Recommendations Assessment, Development and Evaluation system:

Table 7. Grading the Certainty of Evidence and Strength of Recommendations of British Society of Gastroenterology Guidelines

Grading Certainty of Evidence			
High	Confident that the true effect is close to the estimated effect.		
Moderate	Moderately confident in the effect estimate: The true effect is likely close to the estimated effect, but there is a sizeable possibility that it is substantially different.		
Low	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimated effect.		
Grading Recommendations			
Strength	Balance of Benefits and Harms	Applicable Patient Population	Policy Implication
Strong	Confidence that benefits clearly outweigh risks and burden or vice versa.	Applies to most patients in most circumstances.	Only strong recommendations could be considered as quality indicators to guide the development of accountability, reporting, and payment programs.
Conditional	Benefits probably outweigh risks and burden, or vice versa, but there is appreciable uncertainty.	Applies to many patients but may differ depending on circumstances or patients' values and preferences.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Quality indicators

			would have to focus on the fact that adequate deliberation about the management options has taken place.

The British Society of Gastroenterology has issued the recommendations below[8]:

First-line treatments

- All individuals with IBS are advised to engage in regular physical activity (recommendation: strong, quality of evidence: weak).
- First-line dietary advice should be offered to all patients with IBS (recommendation: strong, quality of evidence: weak).
- The use of food elimination diets based on IgG antibodies is not recommended for patients with IBS (recommendation: strong, quality of evidence: moderate).
- Effective treatment for overall IBS symptoms and abdominal pain can be achieved with soluble fiber, such as ispaghula. However, insoluble fiber like wheat bran should be avoided due to the potential exacerbations of symptoms. It's advised to start soluble fiber at a low dose (3–4 g/day) and gradually increase to prevent bloating (recommendation: strong; quality of evidence: moderate).
- A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) can be considered as a secondary dietary therapy for treating global IBS symptoms and abdominal pain. However, its implementation should be overseen by a trained dietitian, and reintroduction of FODMAPs should be based on individual tolerance (recommendation: weak, quality of evidence: very low).
- A gluten-free diet is not recommended for individuals with IBS (recommendation: weak, quality of evidence: very low).
- Probiotics, as a category, might be effective in treating overall IBS symptoms and abdominal pain. While there isn't a specific species or strain recommendation, it's reasonable for patients to try probiotics for up to 12 weeks. If symptoms don't improve, discontinuation is suggested (recommendation: weak, quality of evidence: very low).
- Loperamide may be effective for managing diarrhea in IBS. However, common side effects like abdominal pain, bloating, nausea, and constipation

might affect tolerability. Careful dose titration can help mitigate these effects (recommendation: strong; quality of evidence: very low).'

- Specific antispasmodics could potentially be effective for addressing overall IBS symptoms and abdominal pain. Common side effects include dry mouth, visual disturbances, and dizziness (recommendation: weak, quality of evidence: very low)
- Peppermint oil might offer potential effectiveness in addressing overall IBS symptoms and abdominal pain. However, it's worth noting that gastro-esophageal reflux is a frequently observed side effect (recommendation: weak, quality of evidence: very low).
- Polyethylene glycol could be considered as a possible treatment for constipation in IBS. Yet, it's important to acknowledge that abdominal pain is a common side effect (recommendation: weak; quality of evidence: very low).

Second-line treatments

- Tricyclic antidepressants, utilized as neuromodulators targeting the gut-brain connection, are an effective secondary treatment option for managing overall IBS symptoms and abdominal pain. They can be introduced in either primary or secondary healthcare settings; however, a comprehensive explanation for their use should be provided, and patients must be informed about potential side effects. These antidepressants should be initiated at a low dose (e.g., 10 mg amitriptyline once daily) and gradually titrated to a maximum of 30–50 mg once daily (recommendation: strong, quality of evidence: moderate).
- Selective serotonin reuptake inhibitors, acting as neuromodulators for the gut-brain axis, might be a useful secondary treatment choice for addressing global IBS symptoms. Similar to tricyclic antidepressants, they can be initiated in primary or secondary care, but it's essential to thoroughly counsel on the rationale behind their use and inform patients about potential side effects (recommendation: weak, quality of evidence: low).
- Eluxadoline, a mixed opioid receptor medication, is an effective second-line option for treating IBS with diarrhea in secondary care. However, its use is not recommended for individuals with a history of sphincter of Oddi issues or cholecystectomy, alcohol dependence, pancreatitis, severe liver impairment, and availability might be limited (recommendation: weak, quality of evidence: moderate).
- 5-Hydroxytryptamine 3 receptor antagonists are efficacious second-line treatments for IBS with diarrhea in secondary care. While medications like alosetron and ramosetron might not be available in all countries, ondansetron titrated from 4 mg once daily to a maximum of 8 mg three times a day can serve as a reasonable alternative. Constipation is the primary side effect,

making this drug class particularly effective for IBS with diarrhea (recommendation: weak, quality of evidence: moderate to high).

- The non-absorbable antibiotic rifaximin is an efficacious second-line treatment for IBS with diarrhea in secondary care. Its effect on abdominal pain is limited. While approved for IBS with diarrhea in the USA, its availability is restricted in many regions (recommendation: weak, quality of evidence: moderate).
- Linaclotide, acting as a guanylate cyclase-C agonist, is an effective second-line treatment for IBS with constipation in secondary care. It's likely one of the most effective secretagogues for this condition, although diarrhea is a common side effect (recommendation: strong, quality of evidence: high).
- Lubiprostone, a chloride channel activator, is a successful second-line treatment for IBS with constipation in secondary care. This secretagogue is less likely to induce diarrhea compared to others, but patients should be cautioned about the frequent occurrence of nausea as a side effect (recommendation: strong, quality of evidence: moderate).
- Plecanatide, another guanylate cyclase-C agonist, is an efficacious second-line treatment for IBS with constipation in secondary care. Diarrhea is a common side effect, similar to linaclotide or tenapanor. While approved for IBS with constipation in the USA, it has not been approved yet for the same indication in several countries (recommendation: strong, quality of evidence: high).
- Tenapanor, a sodium-hydrogen exchange inhibitor, is an effective second-line treatment for IBS with constipation in secondary care. Once again, diarrhea is a prevalent side effect. Despite being approved for IBS with constipation in the USA, its availability for this indication is restricted in various countries (recommendation: strong, quality of evidence: high).
- Tegaserod, a 5-Hydroxytryptamine 4 receptor agonist, serves as an effective second-line treatment for IBS with constipation in secondary care. Unfortunately, it's not accessible outside the USA, and diarrhea is a common side effect (recommendation: strong, quality of evidence: moderate).

Management of severe or refractory IBS

- If IBS symptoms are severe or not responding well to treatment, it's advisable to reevaluate the diagnosis and explore targeted investigations (recommendation: weak, evidence: very low).
- A comprehensive interdisciplinary strategy should be adopted for managing severe or treatment-resistant IBS cases (recommendation: weak, evidence: very low).

- It's important to avoid iatrogenic harms that can arise from prescribing opioids, unnecessary surgeries, and employing unproven or unregulated diagnostic or therapeutic methods driven by financial or reputational motives (recommendation: strong, evidence: very low).
- For more severe symptoms, the consideration of combined gut-brain neuromodulators, known as augmentation, is an option, while remaining cautious about the potential risks of serotonin syndrome (recommendation: weak, evidence: very low).

Psychological therapies

- IBS-specific cognitive behavioral therapy has the potential to be an effective treatment for addressing overall IBS symptoms (recommendation: strong, quality of evidence: low).
- Gut-directed hypnotherapy might offer effectiveness in treating overall IBS symptoms (recommendation: strong, quality of evidence: low).
- When symptoms don't show improvement after 12 months of drug-based treatment, it's recommended to contemplate psychological therapies. Referral to these therapies can occur earlier if locally available and in line with patient preferences (recommendation: strong, quality of evidence: low).

1.2.7 Italian guidelines for the management of irritable bowel syndrome Joint Consensus from the Italian Societies of: Gastroenterology and Endoscopy (SIGE), Neurogastroenterology and Motility (SINGEM), Hospital Gastroenterologists and Endoscopists (AIGO), Digestive Endoscopy (SIED), General Medicine (SIMG), Gastroenterology, Hepatology and Pediatric Nutrition (SIGENP) and Pediatrics (SIP) (2023)

The 2023 joint Italian guidelines have opted for the same grading system for evidence and recommendations detailed in table 6.

The Italian Societies of: Gastroenterology and Endoscopy (SIGE), Neurogastroenterology and Motility (SINGEM), Hospital Gastroenterologists and Endoscopists (AIGO), Digestive Endoscopy (SIED), General Medicine (SIMG), Gastroenterology, Hepatology and Pediatric Nutrition (SIGENP) and Pediatrics (SIP) has issued the recommendations below[9]:

- Recommend a dietary approach for patients with IBS. Traditional dietary advice is suggested as a first line approach, while a low FODMAP diet as a second line approach. A gluten free diet is not recommended in patients with IBS (recommendation: strong, quality of evidence: low).

- Recommend soluble but not insoluble fiber supplementation to treat global IBS symptoms (recommendation: strong, quality of evidence: low).
- Recommend the use of probiotics, as a group, for improving overall symptoms or abdominal pain in patients with IBS (recommendation: conditional, quality of evidence: low).
- Suggest the use of polyethylene glycol for the treatment of constipation in patients with IBS-C. The dose should be titrated according to stool consistency (recommendation: conditional, quality of evidence: very low).
- Secretagogues are useful for the treatment of global symptoms and constipation in patients with IBS-C. Diarrhea is a frequent side effect (recommendation: strong, quality of evidence: high).
- Suggest the use of 5-HT4 agonists in selected IBS-C patients who have failed conventional therapy (recommendation: conditional, quality of evidence: low).
- Suggest the use of bile acid sequestrants to treat IBS-D symptoms in case of proven bile acid malabsorption. If testing is not available, in patients with IBS-D, not otherwise manageable with first line treatments, a trial of bile acid sequestrants is advisable (recommendation: conditional, quality of evidence: very low).
- Suggest the use of rifaximin to treat global symptoms in patients with IBS without constipation (recommendation: moderate, quality of evidence: strong).
- Suggest the use of 5-HT3 antagonists for global IBS-D symptoms in patients who have failed conventional therapy (recommendation: conditional, quality of evidence: low).
- Recommend the use of opioid agonists to manage diarrhea in IBS-D (recommendation: conditional, quality of evidence: low).
- Recommend the use of mixed opioid agonists/antagonists to treat global symptoms in IBS-D (recommendation: strong, quality of evidence: high).
- Recommend against the use of fecal microbiota transplantation in patients with IBS (recommendation: strong, quality of evidence: low).
- Recommend the use of antispasmodics for global symptom improvement in patients with IBS (recommendation: conditional, quality of evidence: low).
- Recommend the use of tricyclic antidepressant (TCAs) in adult patients with IBS to induce global relief of symptoms and to treat abdominal pain alone (recommendation: strong, quality of evidence: moderate).

- Recommend the use of selective serotonin reuptake inhibitors (SSRIs) in adult patients with IBS to induce global relief of symptoms (recommendation: conditional, quality of evidence: low).
- Recommend against the use of cannabinoid and endocannabinoid modulators to treat IBS symptoms (recommendation: conditional, quality of evidence: low).
- Recommend against the use of complementary alternative therapies, although some reasonably good quality evidence exists for specific approaches (recommendation: conditional, quality of evidence: low).
- Recommend the use of psychologically directed therapies for the treatment of global symptoms in patients with IBS (recommendation: strong, quality of evidence: low).

1.2.8 Belgian Consensus on Irritable Bowel Syndrome (2022)

The 2022 Belgian community[10] have opted for the following Grading Scheme/Level of Evidence:

Table 8. Belgian Community Grading/Level of Evidence

Code	Quality of evidence	Definition
A	High	Further research is very unlikely to change our confidence in the estimate of effect • Several high-quality studies with consistent results • In special cases: one large, high-quality multicenter trial
B	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate • One high-quality study • Several studies with some limitations
C	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate • One or more studies with severe limitations
D	Very low	Any estimate of effect is very uncertain • Expert opinion • No direct research evidence

		• One or more studies with very severe limitations

The Belgian consensus has issued the recommendations below[10]:

- A fructose reduced diet is effective in the treatment of IBS (Grade C).
- Advise against the gluten-free diet for the management of IBS (Grade C).
- A low FODMAP diet is effective in the treatment of IBS (Grade B).
- A low FODMAP diet is the preferred first-line treatment in IBS (Grade D).
- First-line approach with lifestyle modification is effective in IBS (Grade C).
- Water-soluble fibers are effective in IBS (Grade B).
- Spasmolytics are effective in IBS (Grade B).
- Spasmolytics are the preferred first-line treatment in IBS (Grade B).
- Simethicone in monotherapy is not effective in IBS (Grade D).
- Herbal medicine is effective in IBS (Grade C).
- Bile acid sequestrants are effective for diarrhea in IBS (Grade B).
- Loperamide is effective for diarrhea in IBS but lacks efficacy on pain management (Grade B).
- Mesalazine is not effective in IBS (Grade C).
- Osmotic laxatives are effective for constipation in IBS-C (Grade C).
- Prucalopride is effective for severe constipation in IBS-C patients failing first-line treatment (Grade A).
- Linaclotide is effective for severe constipation and abdominal pain in IBS-C failing first-line treatment (Grade C).
- Assessment of evacuation disorders is useful in the management of IBS-C failing initial treatment (Grade B).
- Biofeedback is effective in IBS-C patients with (suspected or documented) dyssynergic defecation (Grade C).
- Selected probiotics are effective in IBS (Grade C).
- We advise against fecal microbiota transplantation for the treatment of IBS (Grade B).
- Tricyclic antidepressants are effective in IBS (Grade B).
- Selective serotonin reuptake inhibitors are effective in IBS (Grade B).
- Centrally acting opioids are not effective in IBS (Grade D).

- Cognitive behavioral therapy is effective in IBS (Grade B).
- Osteopathy is not effective in IBS (Grade C).

1.2.9 Guidelines on the Management of Irritable Bowel Syndrome Przeglad Gastroenterologiczny (2018)

The 2018 Gastroenterology Review guidelines[17] have opted for the following Grading Scheme/Level of Evidence:

Table 9. Gastroenterology Review Grading/Level of Evidence

Strength of recommendation	
Strong	Benefits clearly outweigh risks and burdens or vice versa. Usually stated as: "we recommend"
Weak	Benefits closely balanced with risks and burden. Usually stated as: "we suggest"
Evidence level (quality of evidence)	
High	One or more well-designed and well-executed randomized controlled trials (RCTs) that yield consistent and directly applicable results. This level also means that further research is very unlikely to change our confidence in the estimate of effect.
Moderate	RCTs with important limitations (i.e., biased assessment of the treatment effect, large loss to follow-up, lack of blinding, unexplained heterogeneity), indirect evidence originating from similar (but not identical) populations of interest, and RCTs with a very small number of participants or observed events. In addition, evidence from well-designed controlled trials without randomization, from well-designed cohort or case-control analytic studies, and from multiple time series with or without intervention is in this category. This level also means that further research will probably have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Observational studies would typically be rated as low quality because of the risk for bias. This level also means that further research is very likely to have an important impact on our confidence in the estimate of effect and will probably change the estimate.

Very low	Evidence is conflicting, of poor quality, or lacking, and hence the balance of benefits and harms cannot be determined. Any estimate of effect is very uncertain as evidence is either unavailable or does not permit a conclusion.

The Gastroenterology Review guidelines has issued the recommendations below[12]:

- Suggest moderate physical exercise of various forms (including yoga) in order to maintain fitness and reduce the overall symptoms of IBS (Recommendation: weak, quality of evidence: very low).
- In order to reduce the overall symptoms of IBS, suggest a reasonable, supervised (physician, dietitian, trainer) weight-loss program to achieve a normal BMI (Recommendation: weak, quality of evidence: very low).
- Suggest: independent exercise sessions, participation in support groups, patient organizations, associations, clubs or psychological consultations in order to develop optimal ways of coping with stress, which may translate into a reduction in overall IBS symptoms (Recommendation: weak, quality of evidence: very low).
- In order to reduce the overall symptoms, suggest a temporary (6-week) diet with a low content of poorly absorbed, easily fermentable oligo-, di-, monosaccharides and polyols (the low-FODMAP diet). Due to the fact that there is insufficient evidence, do not recommend repeating the diet (Recommendation: weak, quality of evidence: very low).
- Do not recommend the use of a gluten-free diet (Recommendation: weak, quality of evidence: very low).
- Do not recommend the use of an elimination diet based on the concentration of antibodies against individual nutrients (Recommendation: weak, quality of evidence: very low).
- In the case of patients benefiting from an elimination diet, individual dietary modifications based on the patient's experience are suggested (Recommendation: weak, quality of evidence: very low).
- In order to reduce the overall symptoms, recommend using a diet rich in soluble fiber in all types of IBS. Due to the nature of the disease, the diet should be used long-term (Recommendation: strong, quality of evidence: moderate).
- The dose of fiber has not been clearly defined. Suggest using 10–25 g fiber daily (Recommendation: weak, quality of evidence: low).

- Due to the proven lack of efficacy, do not recommend the use of insoluble fiber, which may additionally exacerbate pain and abdominal distension (Recommendation: strong, quality of evidence: moderate).
- Recommend using selected peppermint oil preparations to reduce overall symptoms (Recommendation: strong, quality of evidence: moderate).
- So far, the minimum, optimal or maximum duration of use of peppermint oil has not been determined. Based on available studies, suggest using the preparation for 2 to 12 weeks, at a suggested dose of 180 to 225 mg twice daily. The efficacy and safety of longer-term use must be confirmed by tests (Recommendation: weak, quality of evidence: very low).
- Suggest using certain strains or a combination of probiotic strains tested for their efficacy in IBS, rather than probiotics as a group, to reduce overall symptoms of IBS as well as bloating and diarrhea in patients with IBS (Recommendation: weak, quality of evidence: very low).
- Suggest using certain antispasmodics, the efficacy of which in IBS has been confirmed, such as hyoscine and drotaverine (and some unavailable in Poland: otilonium, cimetropium and pinaverium bromides, and dicyclomine) rather than antispasmodics as a group (Recommendation: weak, quality of evidence: very low).
- In order to improve the overall symptoms of IBS, recommend the use of tricyclic antidepressants (TCAs) (Recommendation: strong, quality of evidence: high).
- In order to improve the overall symptoms of IBS, suggest the use of selective serotonin reuptake inhibitors (SSRIs) (Recommendation: weak, quality of evidence: low).
- Suggest using the drugs in the smallest effective doses for 4–12 weeks, although the maximum duration of drug use (regarding their efficacy and safety) has not been clearly defined. If treatment brings additional benefits, it can be used for longer (Recommendation: weak, quality of evidence: very low).
- In the following types of IBS, in order to reduce the overall symptoms and to reduce abdominal bloating and/or diarrhea, recommend a 14-day course of rifaximin α: with predominant diarrhea, with mixed bowel habit and unclassified (Recommendation: strong, quality of evidence: high).
- In the case of the first and second recurrence in patients who have benefited from rifaximin α therapy, recommend repeated treatment in the same pattern. The minimum interval between cycles has not been clearly defined; usually recommend a 4-week interval between successive cycles (Recommendation: strong, quality of evidence: high).

- Suggest using polyethylene glycol preparations to decrease the severity of constipation in patients with constipation-predominant IBS. These drugs do not decrease the overall IBS symptoms (Recommendation: weak, quality of evidence: low).
- Suggest the use of loperamide to decrease severity of diarrhea in patients with diarrhea-predominant IBS. The drug does not decrease overall symptoms of IBS (Recommendation: weak, quality of evidence: very low).
- In constipation-predominant IBS linaclotide reduces overall symptoms (quality of evidence: high).
- In constipation-predominant IBS plecanatide reduces overall symptoms (quality of evidence: moderate).
- In constipation-predominant IBS, lubiprostone reduces overall symptoms (quality of evidence: moderate).
- In women with diarrhea-predominant IBS alosetron reduces overall symptoms (quality of evidence: low).
- In diarrhea-predominant IBS eluxadoline reduces overall symptoms (quality of evidence: moderate).
- Recommend against mesalazine for improvement of overall symptoms of IBS due to proven lack of efficacy in this indication (Recommendation: strong, quality of evidence: high).
- There is not enough evidence to make unambiguous recommendations concerning FMT. Do not recommend the use of FMT in IBS (Recommendation: weak, quality of evidence: very low).

1.2.10 The Japanese Society of Gastroenterology Evidence-Based Clinical Practice Guidelines for Irritable Bowel Syndrome (2021)

The 2021 Japanese Society of Gastroenterology guidelines[11] have opted for the following Grading Scheme/Level of Evidence:

Table 10. Japanese Society of Gastroenterology Grading/Level of Evidence

Strength of recommendation	
Strong	Benefits clearly outweigh risks and burden or vice versa. Usually stated as: “we recommend”
Weak	Benefits closely balanced with risks and burden. Usually stated as: “we suggest”
Evidence level (quality of evidence)	

High	A
Moderate	B
Low	C
Very low	D

The Japanese Society of Gastroenterology guidelines has issued the recommendations below[11]:

- Eliminating foods that exacerbate IBS symptoms, such as lipids, caffeine, spicy food, and milk and dairy products, is effective in managing IBS. Dietary therapy is recommended for IBS (Weak recommendation, evidence level B).
- Exercise therapy under proper instruction improves IBS symptoms (Weak recommendation, evidence level B). There is no clear evidence for the utility of other behavioral modifications, such as eliminating alcohol and smoking or getting adequate sleep.
- Bulking polymer intake or dietary fiber intake is an effective means of treating IBS. Bulking polymers or dietary fiber is recommended for IBS (Strong recommendation, evidence level A).
- Gastrointestinal modifiers are effective in treating IBS. Gastrointestinal motility modifiers are recommended for IBS (Weak recommendation, evidence level B).
- Anticholinergic agents are effective in some patients with IBS. Anticholinergic agents are recommended for some patients with IBS (Weak recommendation, evidence level B).
- Probiotics are effective in treating IBS. Probiotics are recommended for IBS (Strong recommendation, evidence level A).
- 5-HT3 receptor antagonists are effective on IBS-D. 5-HT3 receptor antagonists are recommended for IBS-D (Strong recommendation, evidence level A).
- Anti-diarrheal agents are effective in some patients with IBS-D. Anti-diarrheal agents are recommended for some patients with IBS-D (Weak recommenda- tion, evidence level C).
- Intestinal secretagogues are effective and are rec- ommended for use in patients with IBS-C (Strong recommendation, evidence level A).
- Bile acids and an ileal bile acid transporter inhibitor are suggested to be useful for patients with IBS-C (Weak recommendation, evidence level B).
- 5-HT4 agonists are effective in treating IBS-C. 5-HT4 agonists are recommended for IBS-C (Weak recommendation, evidence level B).

- Osmotic laxatives are effective for some patients with IBS-C. Osmotic laxatives are recommended for some patients with IBS-C (Weak recommendation, evidence level C)
- Stimulant laxatives are effective in some patients with IBS-C. In principle, on-demand use of stimulant laxatives is recommended for some patients with IBS-C (Weak recommendation, evidence level D).
- Antidepressants are useful for IBS. Tricyclic antide- pressants and selective serotonin reuptake inhibitors are recommended for patients with IBS depending on the pathophysiology, taking into consideration side effects (Weak recommendation, evidence level A).
- Anxiolytics are useful for treating IBS. Relieving anxiety is related to improving the symptoms of IBS in highly anxious patients. Anxiolytics are recommended for patients with IBS depending on the pathophysiology. Anxiolytics should be used for a short period while taking into account the risk of dependency (Weak recommendation, evidence level B).
- Psychotherapy is effective in treating patients with IBS. Psychotherapy is recommended for IBS patients (Strong recommendation, evidence level B).
- Kampo medicine (traditional Japanese medicine) is effective in treating IBS. Kampo agents are recommended for IBS (Weak recommendation, evidence level C).
- Anti-allergic agents are effective in treating IBS. Anti-allergic agents are recommended for in treating some patients with IBS (Strong recommendation, evidence level A).
- Some non-absorbable antimicrobial agents are effective as a treatment for IBS (Weak recommendation, evidence level A).
- Peppermint oil is effective in treating IBS. Of all comprehensive alternative medicines, only peppermint oil is recommended for treating IBS (Weak recommendation, evidence level A).
- Narcotics are not effective in alleviating abdominal pain in IBS. No narcotics are recommended for abdominal pain in IBS (Weak recommendation, evidence level C).
- IBS patients are at risk of many diseases and impaired QOL. It is beneficial to prevent IBS patients from leaving without treatment (Weak recommendation, evidence level C).
- There is little evidence for the usefulness of anti-psychotics or mood stabilizers in patients with IBS. Anti-psychotics and mood stabilizers may be used in IBS

patients to control abdominal pain or mental state in severe cases, but there are various side effects. Further studies are needed.

- FMT is being investigated as a treatment for IBS. Further studies are needed to evaluate the efficacy of FMT in IBS.

Section 2.0 Drug Therapy in Irritable Bowel Syndrome (IBS)

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs to delist due to withdrawal from the market among others, and the fourth contains drugs that have been newly approved by the FDA and/or EMA, but have not been SFDA registered yet.

2.1 Additions

No new drugs have been added for the treatment of irritable bowel syndrome since March 2020.

2.2 Modifications

The following modifications and adjustments have been implemented since the 2020 report:

Table 11. Prescribing Edits (PE) Modifications for Irritable Bowel Syndrome (IBS) Medications

Drugs	PE modifications
Hyoscine butylbromide	AGE was added: not recommended for children < 6 years old
Imipramine hydrochloride	PA removed
Loperamide	AGE was added: contraindicated in children < 2 years old MD removed: can be bought OTC
Mebeverine hydrochloride	AGE was added: not recommended in children < 18 years old
Paroxetine	AGE was added: children < 18 years old should not normally take paroxetine

2.3 Delisting

The medications below are no longer SFDA registered[18], therefore, it is recommended to delist the following drugs from CHI formulary:

- Amitriptyline hydrochloride
- Trimebutine
- Vitamins, folic acid, pantothenic acid, calcium, lactic ferments (lactobacillus acidophilus & sporogenes, bifidobacterium bifidum, longum & infantis)

2.4 Other Drugs

Tenepanor is **newly approved** by the FDA and/or the EMA; however, it has **not yet been registered by the SFDA**. On the other hand, tegaserod has been approved for years, but is also not SFDA registered.

Tenapanor (Ibsrela®)

Tenapanor was approved by the FDA in 2019 for the treatment of irritable bowel syndrome with constipation (IBS-C) in adults. The recommended dosage of Tenapanor in adults is 50 mg orally twice daily. It is contraindicated in pediatric patients less than 6 years of age and patients with known or suspected mechanical gastrointestinal obstruction. Patients may experience severe diarrhea. If severe diarrhea occurs, suspend dosing and rehydrate patient[19].

Tegaserod (Zelnorm®)

Tegaserod was approved by the FDA in 2002. Tegaserod is a serotonin-4 (5-HT4) receptor agonist indicated for the treatment of adult women less than 65 years of age with irritable bowel syndrome with constipation (IBS-C). Safety and effectiveness in men with IBS-C have not been established. The recommended dose for adult women under 65 years old is 6 mg to be taken orally twice a day, at least 30 minutes prior to meals. If symptoms are not adequately managed after 4 to 6 weeks of treatment, discontinue the use of Tegaserod[20].

Section 3.0 Key Recommendations Synthesis

- The treatment of irritable bowel syndrome (IBS) is typically based on the severity of symptoms and can vary from person to person. The treatment recommendations for IBS often include a combination of dietary and lifestyle changes, medication, and psychological therapies[6–10].
- According to the guidelines, consider dietary changes, including traditional dietary advice, and potentially a low FODMAP diet, but under the guidance of a healthcare professional[6,8–10,13].
- Soluble fiber can be effective in managing IBS symptoms, while insoluble fiber should be avoided[6,8]. A gluten-free diet is not recommended for IBS[6,10, 14].
- Engaging in regular physical activity and considering stress management techniques is essential for symptom management of IBS[7,8].
- Treatment should be individualized based on the patient's specific symptoms and response to therapies[6–10,13,16].
- According to the guidelines, for **IBS-D treatment:**
  - **Eluxadoline** may be used, but is contraindicated in certain cases[7,8, 14 ,15].
  - **Rifaximin** can be considered, and retreatment may be necessary for recurrent symptoms[6,7,9, 14, 15].
  - **Alosetron** is suggested for symptom relief[6,8,15].
  - **Loperamide** may be considered[8,15,7,10, 14].
- According to the guidelines, for **IBS-C treatment:**
  - **Linaclotide** is recommended in severe cases and upon failure of first line options[8,10,16].
  - **Lubiprostone**; acts as a chloride channel activator, serves as an effective secondary treatment option for constipation-predominant IBS in clinical settings. Unlike some other options, it has a lower likelihood of causing diarrhea. However, it's important to advise patients about the relatively frequent occurrence of nausea as a side effect[16].
  - **Plecanatide**; functions as a guanylate cyclase-C agonist, proves to be an effective secondary treatment choice for constipation-predominant IBS in clinical settings. However, it's important to note that diarrhea is a frequent side effect, akin to linaclotide or tenapanor. While it has gained approval for treating IBS with constipation in the United States, its approval for the

same indication is still pending in several other countries. can be considered[16].

- **Tegaserod** is an option, primarily for women under 65 without cardiovascular risk factors[8,16].
- **Polyethylene glycol (PEG) laxatives** may be used[9,16].
- **Prucalopride** is recommended for severe constipation[10].
- **Osmotic laxatives** may be considered[7].
- **Tenapanor;** an inhibitor of the sodium-hydrogen exchange, is a potent secondary treatment option for constipation-predominant IBS in a clinical setting. It's worth noting that diarrhea remains a commonly observed side effect. Although it has received approval for treating IBS with constipation in the United States, its accessibility is limited in numerous countries[8,16].

- In general, medications for management of global IBS symptoms include:
  - **Antispasmodics** may be considered but with limited evidence[7–9,15,16].
  - Recommend the utilization of antispasmodic agents in patients with IBS-D, but note the absence of data for FDr[14].
  - **Tricyclic antidepressants (TCAs)** can be effective [7–9,15,16].
  - **Selective serotonin reuptake inhibitors (SSRIs)** may be used with caution but there is no consensus among guidelines; some suggest its use while others do not recommend it [7–9, 14-16].
  - Recommend the use of 5-HT3 antagonists (alosetron, ondansetron, ramosetron) in treating patients with IBS-D to improve IBS symptoms, but highlight the lack of evidence for FDr[14].
- Probiotics may be considered for a maximum duration of 12 weeks, but specific strains should be chosen[6,8–10].
- Peppermint oil might offer potential effectiveness in symptom relief[6,8].
- Fecal microbiota transplantation (FMT) is not recommended for IBS[6,9, 14].
- Simethicone in monotherapy is not effective in IBS[10].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Irritable Bowel Syndrome (IBS) report** and aims to provide recommendations to aid in the management of irritable bowel syndrome (IBS). It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the

management of individual patients with Irritable Bowel Syndrome (IBS). Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. Irritable Bowel Syndrome (IBS) Scope

Section	Rationale/Updates
Addition of a new section: AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome with Diarrhea (2022)[15]	In patients with IBS-D, the AGA suggests using eluxadoline Implementation remark: eluxadoline is contraindicated in patients without a gallbladder or those who drink more than 3 alcoholic beverages per day. In patients with IBS-D, the AGA suggests using rifaximin. In patients with IBS-D with initial response to rifaximin who develop recurrent symptoms, the AGA suggests retreatment with rifaximin. In patients with IBS-D, the AGA suggests using alosetron. In patients with IBS-D, the AGA suggests using loperamide. In patients with IBS, the AGA suggests using TCAs. In patients with IBS, the AGA suggests against using SSRIs. In patients with IBS, the AGA suggests using antispasmodics.
Addition of a new section: AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome with Constipation (2022)[16]	In patients with IBS-C, the AGA suggests using tenapanor. In patients with IBS-C, the AGA suggests using plecanatide. In patients with IBS-C, the AGA recommends using linaclotide. In patients with IBS-C, the AGA suggests using tegaserod Implementation remark: Tegaserod was reapproved for women under the age of 65 years without a history of cardiovascular ischemic events (such as myocardial infarction, stroke, TIA, or angina). In patients with IBS-C, the AGA suggests using lubiprostone. In patients with IBS-C, the AGA suggests using PEG laxatives. In patients with IBS, the AGA suggests using TCAs. In patients with IBS, the AGA suggests against using SSRIs. In patients with IBS, the AGA suggests using antispasmodics.
Addition of a new	We recommend a limited trial of a low FODMAP diet in patients with IBS to improve global

section: ACG Clinical Guideline: Management of Irritable Bowel Syndrome (2020)[6]	IBS symptoms. We suggest that soluble, but not insoluble, fiber be used to treat global IBS symptoms. We recommend against the use of antispasmodics for the treatment of global IBS symptoms. We suggest the use of peppermint to provide relief of global IBS symptoms. We suggest against probiotics for the treatment of global IBS symptoms. We suggest against PEG products to relieve global IBS symptoms in those with IBS-C. We recommend the use of chloride channel activators to treat global IBS-C symptoms. We recommend the use of guanylate cyclase activators to treat global IBS-C symptoms. We suggest that the 5-HT4 agonist tegaserod be used to treat IBS-C symptoms in women younger than 65 years with > 1 cardiovascular risk factors who have not adequately responded to secretagogues. We do not suggest the use of bile acid sequestrants to treat global IBS-D symptoms. We recommend the use of rifaximin to treat global IBS-D symptoms. We recommend that alosetron be used to relieve global IBS-D symptoms in women with severe symptoms who have failed conventional therapy. We suggest that mixed opioid agonists/antagonists be used to treat global IBS-D symptoms. We recommend that tricyclic antidepressants be used to treat global symptoms of IBS. We suggest that gut-directed psychotherapies be used to treat global IBS symptoms. Using currently available evidence, we recommend against the use of fecal transplant for the treatment of global IBS symptoms.
Addition of a new section: AGA Clinical Practice Update on the Role of Diet in Irritable Bowel	Dietary advice is ideally prescribed to patients with IBS who have insight into their meal-related gastrointestinal symptoms and are motivated to make the necessary changes. To optimize the quality of teaching and clinical response, referral to a registered dietitian nutritionist (RDN) should be made to patients who are willing to collaborate with a RDN and patients who are not able to implement beneficial dietary changes on their own. If a gastrointestinal RDN is not available, other resources can assist with implementation of diet

Syndrome: Expert Review (2022)[13]	interventions. Patients with IBS who are poor candidates for restrictive diet interventions include those consuming few culprit foods, those at risk for malnutrition, those who are food insecure, and those with an eating disorder or uncontrolled psychiatric disorder. Routine screening for disordered eating or eating disorders by careful dietary history is critical because they are common and often overlooked in gastrointestinal conditions. Specific diet interventions should be attempted for a predetermined length of time. If there is no clinical response, the diet intervention should be abandoned for another treatment alternative, for example, a different diet, medication, or other form of therapy. In preparation for a visit with a RDN, patients should provide dietary information that will assist in developing an individualized nutrition care plan. Soluble fiber is efficacious in treating global symptoms of IBS. The low-FODMAP diet is currently the most evidence- based diet intervention for IBS. Healthy eating advice as described by the National Institute of Health and Care Excellence Guidelines, among others, also offers benefit to a subset of patients with IBS. The low-FODMAP diet consists of the following 3 phases: 1) restriction (lasting no more than 4–6 weeks) 2) reintroduction of FODMAP foods 3) personalization based on results from reintroduction. Although observational studies found that most patients with IBS improve with a gluten-free diet, randomized controlled trials have yielded mixed results. There is limited data showing that selected biomarkers can predict response to diet interventions in patients with IBS, but there is insufficient evidence to support their routine use in clinical practice.
Addition of a new section: Functional bowel disorders with	o Recommend the utilization of antispasmodic agents in patients with IBS-D, but note the absence of data for FDr (Weak recommendation, low level of evidence). o Recommend the use of loperamide in patients with IBS-D or FDr (Strong recommendation, low level of evidence).

diarrhea: Clinical guidelines of the United European Gastroenterology and European Society for Neurogastroenterology and Motility **(2022)**	o Recommend the utilization of rifaximin in patients with IBS-D, acknowledging that the therapeutic gain over placebo may be limited. Limited evidence supports the efficacy of rifaximin in the treatment of FDr (Strong recommendation, high level of evidence). o Recommend the use of probiotics that may enhance overall symptoms and alleviate diarrhea in some patients with IBS-D, but highlight the lack of evidence for FDr (Conditional recommendation, low level of evidence). o Recommend against the use of mesalazine in patients with IBS-D or FDr (Strong recommendation, moderate level of evidence). o Recommend the use of bile acid sequestrants in patients with confirmed bile acid diarrhea. If testing is unavailable, consider a trial of a bile acid sequestrant in patients with persistent unexplained chronic diarrhea (Moderate recommendation, moderate level of evidence). o Recommend the short-term usefulness of a low FODMAPs diet in patients with IBS-D when other measures have failed, but emphasize the absence of evidence for FDr (Strong recommendation, low level of evidence). o Recommend against a gluten-free diet for patients with IBS-D, with no evidence supporting FDr (Strong recommendation, low level of evidence). o Recommend gut-directed psychological therapies as an alternative treatment in patients with IBS-D, but stress the lack of evidence for FDr (Strong recommendation, low level of evidence). o Recommend against the use of fecal microbiota transplantation in patients with IBS-D or FDr (Strong recommendation, low level of evidence). o Recommend the use of eluxadoline for treating patients with IBS-D, with no evidence supporting FDr (Strong recommendation, high level of evidence). o Recommend the use of TCAs for treating patients with IBS-D, despite the absence of evidence for FDr (Consensus). o Recommend against the use of SSRIs for treating patients with IBS-D or FDr

	(Conditional recommendation, very low quality of evidence). o Recommend the use of 5-HT3 antagonists (alosetron, ondansetron, ramosetron) in treating patients with IBS-D to improve IBS symptoms, but highlight the lack of evidence for FDr (Strong recommendation, moderate level of evidence).
Addition of a new section: British Society of Gastroenterology guidelines on the management of irritable bowel syndrome (2021)[8]	**First-line treatments:** All patients with IBS should be advised to take regular exercise. First-line dietary advice should be offered to all patients with IBS. Food elimination diets based on IgG antibodies are not recommended in patients with IBS. Soluble fiber, such as ispaghula, is an effective treatment for global symptoms and abdominal pain in IBS, but insol- uble fiber (eg, wheat bran) should be avoided as it may exacerbate symptoms. Soluble fiber should be commenced at a low dose (3–4 g/day) and built up gradually to avoid bloating. A diet low in fermentable oligosaccharides, disaccharides and monosaccharides and polyols, as a second-line dietary therapy, is an effective treatment for global symptoms and abdominal pain in IBS, but its implementation should be supervised by a trained dietitian and fermentable oligosac- charides, disaccharides and monosaccharides and polyols should be reintroduced according to tolerance. A gluten-free diet is not recommended in IBS. Probiotics, as a group, may be an effective treatment for global symptoms and abdominal pain in IBS, but it is not possible to recommend a specific species or strain. It is reasonable to advise patients wishing to try probiotics to take them for up to 12 weeks, and to discontinue them if there is no improvement in symptoms. Loperamide may be an effective treatment for diarrhea in IBS. However, abdominal pain, bloating, nausea and consti- pation are common, and may limit tolerability. Titrating the dose carefully may avoid this. Certain antispasmodics may be an effective treatment for global symptoms and abdominal pain in IBS. Dry mouth, visual disturbance and dizziness are common side effects. Peppermint oil may be an effective treatment for global symptoms and abdominal pain in

	IBS. Gastro-oesophageal reflux is a common side effect. Polyethylene glycol may be an effective treatment for consti- pation in IBS. Abdominal pain is a common side effect. **Second-line treatments:** Tricyclic antidepressants used as gut-brain neuromodulators are an effective second-line drug for global symptoms and abdominal pain in IBS. They can be initiated in primary or secondary care, but careful explanation as to the rationale for their use is required, and patients should be counselled about their side-effect profile. They should be commenced at a low dose (eg, 10 mg amitriptyline once a day) and titrated slowly to a maximum of 30–50 mg once a day. Selective serotonin reuptake inhibitors used as gut-brain neuromodulators may be an effective second-line drug for global symptoms in IBS. As with tricyclic antidepressants, they can be initiated in primary or secondary care, but careful explanation as to the rationale for their use is required, and patients should be counselled about their side-effect profile (recommendation: weak, quality of evidence: low). Eluxadoline, a mixed opioid receptor drug, is an efficacious second-line drug for IBS with diarrhea in secondary care. It is contraindicated in patients with prior sphincter of Oddi problems or cholecystectomy, alcohol dependence, pancreatitis or severe liver impairment, and lack of availability may limit its use. 5-Hydroxytryptamine 3 receptor antagonists are efficacious second-line drugs for IBS with diarrhea in secondary care. Alosetron and ramosetron are unavailable in many coun- tries; ondansetron titrated from a dose of 4 mg once a day to a maximum of 8 mg three times a day is a reasonable alterna- tive. Constipation is the most common side effect. This drug class is likely the most efficacious for IBS with diarrhea. The non-absorbable antibiotic rifaximin is an efficacious second-line drug for IBS with diarrhea in secondary care, although its effect on abdominal pain is limited. The drug is licensed for IBS with diarrhea in the USA but is not avail- able for this indication in many countries. Linaclotide, a guanylate cyclase-C agonist, is an efficacious second-line drug for IBS with

	constipation in secondary care. It is likely to be the most efficacious secretagogue available for IBS with constipation, although diarrhea is a common side effect. Lubiprostone, a chloride channel activator, is an efficacious second-line drug for IBS with constipation in secondary care. This secretagogue is less likely to cause diarrhea than others. However, patients should be warned that nausea is a frequent side effect. Plecanatide, another guanylate cyclase-C agonist, is an efficacious second-line drug for IBS with constipation in secondary care. Diarrhea is a common side effect and is no less likely than with linaclotide or tenapanor. Although the drug is licensed for IBS with constipation in the USA, it is not yet available for this indication in many countries. Tenapanor, a sodium-hydrogen exchange inhibitor, is an efficacious second-line drug for IBS with constipation in secondary care. Again, diarrhea is a frequent side effect. Although the drug is licensed for IBS with constipation in the USA, it is not yet available for this indication in many countries. Tegaserod, a 5-Hydroxytryptamine 4 receptor agonist, is an efficacious second-line drug for IBS with constipation in secondary care but is unavailable outside the USA. Diarrhea is a common side effect. **Management of severe or refractory IBS** Severe or refractory IBS symptoms should prompt a review of the diagnosis, with consideration of further targeted investigation. Severe or refractory IBS should be managed with an integrated multi-disciplinary approach. Iatrogenic harms due to opioid prescribing, unnecessary surgery and unproven unregulated diagnostic or therapeutic approaches incentivized by financial or reputational gain should be avoided. Use of combination gut-brain neuromodulators, termed augmentation, may be considered for more severe symptoms, with vigilance for risks of serotonin syndrome. **Psychological therapies** IBS-specific cognitive behavioral therapy may be an efficacious treatment for global

	symptoms in IBS. Gut-directed hypnotherapy may be an efficacious treatment for global symptoms in IBS. Psychological therapies should be considered when symptoms have not improved after 12 months of drug treatment. Referral can be made at an earlier stage, if accessible locally, and based on patient preference.
Addition of a new section: Italian guidelines for the management of irritable bowel syndrome Joint Consensus from the Italian Societies of: Gastroenterology and Endoscopy (SIGE), Neurogastroenterology and Motility (SINGEM), Hospital Gastroenterologists and Endoscopists (AIGO), Digestive Endoscopy (SIED), General Medicine (SIMG), Gastroenterology, Hepatology and Pediatric Nutrition (SIGENP) and Pediatrics (SIP) (2023)[9]	We recommend for a dietary approach for patients with IBS. Traditional dietary advice is suggested as first line approach, while a low FODMAP diet as a second line approach. A gluten free diet is not recommended in patients with IBS. We recommend for soluble but not insoluble fiber supplementation to treat global IBS symptoms. We recommend for the use of probiotics, as a group, for improving overall symptoms or abdominal pain in patients with IBS. We suggest for the use of polyethylene glycol for the treatment of constipation in patients with IBS-C. The dose should be titrated according to stool consistency. Secretagogues are useful for the treatment of global symptoms and constipation in patients with IBS-C. Diarrhea is a frequent side effect. We suggest for the use of 5-HT4 agonists in selected IBS-C patients who have failed conventional therapy. We suggest for the use of bile acid sequestrants to treat IBS-D symptoms in case of proven bile acid malabsorption. If testing is not available, in patients with IBS-D, not otherwise manageable with first line treatments, a trial of bile acid sequestrants is advisable. We suggest for the use of rifaximin to treat global symptoms in patients with IBS without constipation. We suggest for the use of 5-HT3 antagonists for global IBS-D symptoms in patients who have failed conventional therapy. We recommend for the use of opioid agonists to manage diarrhea in IBS-D. We recommend for the use of mixed opioid agonists/antagonists to treat global symptoms in IBS-D.

	We recommend against the use of fecal microbiota transplantation in patients with IBS. We recommend for the use of antispasmodics for global symptom improvement in patients with IBS. We recommend for the use of tricyclic antidepressant (TCAs) in adult patients with IBS to induce global relief of symptoms and to treat abdominal pain alone1. We recommend for the use of selective serotonin reuptake inhibitors (SSRIs) in adult patients with IBS to induce global relief of symptoms. We recommend against the use of cannabinoid and endocannabinoid modulators to treat IBS symptoms. We recommend against the use of complementary alternative therapies, although some reasonably good quality evidence exists for specific approaches. We recommend for the use of psychologically directed therapies for the treatment of global symptoms in patients with IBS.
Addition of a new section: Belgian consensus on irritable bowel syndrome (2022)[10]	A fructose reduced diet is effective in the treatment of IBS. We advise against the gluten-free diet for the management of IBS. A low FODMAP diet is effective in the treatment of IBS. A low FODMAP diet is the preferred first-line treatment in IBS. First-line approach with lifestyle modification is effective in IBS. Water-soluble fibers are effective in IBS. Spasmolytics are effective in IBS. Spasmolytics are the preferred first-line treatment in IBS. Simethicone in monotherapy is not effective in IBS. Herbal medicine is effective in IBS. Bile acid sequestrants are effective for diarrhea in IBS. Loperamide is effective for diarrhea in IBS but lacks efficacy on pain management. H1-receptor antagonists are effective in non-constipated IBS. Mesalazine is not effective in IBS.

	Osmotic laxatives are effective for constipation in IBS-C. Prucalopride is effective for severe constipation in IBS-C patients failing first-line treatment. Linaclotide is effective for severe constipation and abdominal pain in IBS-C failing first-line treatment. Assessment of evacuation disorders is useful in the management of IBS-C failing initial treatment. Biofeedback is effective in IBS-C patients with (suspected or documented) dyssynergic defecation. Selected probiotics are effective in IBS. We advise against fecal microbiota transplantation for the treatment of IBS. Tricyclic antidepressants are effective in IBS. Selective serotonin reuptake inhibitors are effective in IBS. Centrally-acting opioids are not effective in IBS. Cognitive behavioral therapy is effective in IBS. Osteopathy is not effective in IBS.
Addition of a new section: Guidelines on the management of irritable bowel syndrome (2018)[12]	We suggest moderate physical exercise of various forms (including yoga) in order to maintain fitness and reduce the overall symptoms of IBS. In order to reduce the overall symptoms of IBS, we suggest a reasonable supervised (physician, dietitian, trainer) weight-loss program to achieve a normal BMI. We suggest: independent exercise sessions, participation in support groups, patient organizations, associations, clubs or psychological consultations in order to develop optimal ways of coping with stress, which may translate into a reduction in overall IBS symptoms. In order to reduce the overall symptoms, we suggest a temporary (6-week) diet with a low content of poorly absorbed, easily fermentable oligo-, di-, monosaccharides and polyols (the low-FODMAP diet). Due to the fact that there is insufficient evidence, we do not recommend repeating the diet. We do not recommend the use of a gluten-free diet.

	We do not recommend the use of an elimination diet based on the concentration of antibodies against individual nutrients. In the case of patients benefiting from an elimination diet, individual dietary modifications based on the patient's experience are suggested. In order to reduce the overall symptoms, we recommend using a diet rich in soluble fiber in all types of IBS. Due to the nature of the disease, the diet should be used long-term. The dose of fiber has not been clearly defined. We suggest using 10–25 g fiber daily. Due to the proven lack of efficacy, we do not recommend the use of insoluble fiber, which may additionally exacerbate pain and abdominal distension. We recommend using selected peppermint oil preparations to reduce overall symptoms. So far, the minimum, optimal or maximum duration of use of peppermint oil has not been determined. Based on available studies, we suggest using the preparation for 2 to 12 weeks. The efficacy and safety of longer-term use must be confirmed by tests. There is not sufficient evidence to make a recommendation regarding STW 5. Taking into consideration mode of action and efficacy in other indications, this product can be helpful in defined clinical situations. We suggest using certain strains or a combination of probiotic strains tested for their efficacy in IBS, rather than probiotics as a group, to reduce overall symptoms of IBS as well as bloating and diarrhea in patients with IBS. We suggest using certain antispasmodics, the efficacy of which in IBS has been confirmed, such as hyoscine and drotaverine (and some unavailable in Poland: otilonium, cimetropium and pinaverium bromides, and dicyclomine) rather than antispasmodics as a group. In order to improve the overall symptoms of IBS, we recommend the use of tricyclic antidepressants (TCAs). In order to improve the overall symptoms of IBS, we suggest the use of selective serotonin reuptake inhibitors (SSRIs). We suggest using the drugs in the smallest effective doses for 4–12 weeks, although the maximum duration of drug use (regarding their efficacy and safety) has not been clearly

	defined. If treatment brings additional benefits, it can be used for longer. In the following types of IBS, in order to reduce the overall symptoms and to reduce abdominal bloating and/or diarrhea, we recommend a 14-day course of rifaximin α: with predominant diarrhea, with mixed bowel habit and unclassified. In the case of the first and second recurrence, in patients who have benefited from rifaximin α therapy, we recommend repeated treatment in the same pat- tern. The minimum interval between cycles has not been clearly defined; we recommend a 4-week interval between successive cycles. We suggest using polyethylene glycol preparations to decrease the severity of constipation in patients with constipation-predominant IBS. These drugs do not decrease the overall IBS symptoms. We suggest the use of loperamide to decrease severity of diarrhea in patients with diarrhea-predominant IBS. The drug does not decrease overall symptoms of IBS. In constipation-predominant IBS linaclotide reduces overall symptoms. In constipation-predominant IBS plecanatide reduces overall symptoms. In constipation-predominant IBS, lubiprostone reduces overall symptoms. In women with diarrhea-predominant IBS alosetron reduces overall symptoms. In diarrhea-predominant IBS eluxadoline reduces overall symptoms. We recommend against mesalazine for improvement of overall symptoms of IBS due to proven lack of efficacy in this indication. There is not enough evidence to make unambiguous recommendations concerning FMT. We do not recommend the use of FMT in IBS.
Addition of a section: The Japanese Society of Gastroenterology Evidence-based clinical practice guidelines for irritable bowel	Eliminating foods that exacerbate IBS symptoms, such as lipids, caffeine, spicy food, and milk and dairy products, is effective in managing IBS. Dietary therapy is recommended for IBS (Weak recommendation, evidence level B). Exercise therapy under proper instruction improves IBS symptoms (Weak recommendation, evidence level B). There is no clear evidence for the utility of other behavioral modifications, such as eliminating alcohol and smoking or getting adequate

syndrome (2021)[11]	sleep. Bulking polymer intake or dietary fiber intake is an effective means of treating IBS. Bulking polymers or dietary fiber is recommended for IBS (Strong recommendation, evidence level A). Gastrointestinal modifiers are effective in treating IBS. Gastrointestinal motility modifiers are recommended for IBS (Weak recommendation, evidence level B). Anticholinergic agents are effective in some patients with IBS. Anticholinergic agents are recommended for some patients with IBS (Weak recommendation, evidence level B). Probiotics are effective in treating IBS. Probiotics are recommended for IBS (Strong recommendation, evidence level A). 5-HT3 receptor antagonists are effective on IBS-D. 5-HT3 receptor antagonists are recommended for IBS-D (Strong recommendation, evidence level A). Anti-diarrheal agents are effective in some patients with IBS-D. Anti-diarrheal agents are recommended for some patients with IBS-D (Weak recommendation, evidence level C). Intestinal secretagogues are effective and are recommended for use in patients with IBS-C (Strong recommendation, evidence level A). Bile acids and an ileal bile acid transporter inhibitor are suggested to be useful for patients with IBS-C (Weak recommendation, evidence level B). 5-HT4 agonists are effective in treating IBS-C. 5-HT4 agonists are recommended for IBS-C (Weak recommendation, evidence level B). Osmotic laxatives are effective for some patients with IBS-C. Osmotic laxatives are recommended for some patients with IBS-C (Weak recommendation, evidence level C) Stimulant laxatives are effective in some patients with IBS-C. In principle, on-demand use of stimulant laxatives is recommended for some patients with IBS-C (Weak recommendation, evidence level D). Antidepressants are useful for IBS. Tricyclic antidepressants and selective serotonin reuptake inhibitors are recommended for patients with IBS depending on the pathophysiology, taking into consideration side effects (Weak recommendation, evidence

	level A). Anxiolytics are useful for treating IBS. Relieving anxiety is related to improving the symptoms of IBS in highly anxious patients. Anxiolytics are recommended for patients with IBS depending on the pathophysiology. Anxiolytics should be used for a short period while taking into account the risk of dependency (Weak recommendation, evidence level B). Psychotherapy is effective in treating patients with IBS. Psychotherapy is recommended for IBS patients (Strong recommendation, evidence level B). Kampo medicine (traditional Japanese medicine) is effective in treating IBS. Kampo agents are recommended for IBS (Weak recommendation, evidence level C). Anti-allergic agents are effective in treating IBS. Anti-allergic agents are recommended for in treating some patients with IBS (Strong recommendation, evidence level A). Some non-absorbable antimicrobial agents are effective as a treatment for IBS (Weak recommendation, evidence level A). Peppermint oil is effective in treating IBS. Of all comprehensive alternative medicines, only peppermint oil is recommended for treating IBS (Weak recommendation, evidence level A). Narcotics are not effective in alleviating abdominal pain in IBS. No narcotics are recommended for abdominal pain in IBS (Weak recommendation, evidence level C). IBS patients are at risk of many diseases and impaired QOL. It is beneficial to prevent IBS patients from leaving without treatment (Weak recommendation, evidence level C). There is little evidence for the usefulness of anti-psychotics or mood stabilizers in patients with IBS. Anti-psychotics and mood stabilizers may be used in IBS patients to control abdominal pain or mental state in severe cases, but there are various side effects. Further studies are needed. FMT is being investigated as a treatment for IBS. Further studies are needed to evaluate the efficacy of FMT in IBS.

Appendix C. PubMed Search Methodology Terms

The following PubMed Search Methodology was used:

Query	Filters	Search Details	Results
((((((((Irritable Bowel Syndrome[MeSH Terms]) OR (Irritable Bowel Syndromes[Title/Abstract])) OR (Syndrome, Irritable Bowel[Title/Abstract])) OR (Syndromes, Irritable Bowel[Title/Abstract])) OR (Colon, Irritable[Title/Abstract])) OR (Irritable Colon[Title/Abstract])) OR (Colitis, Mucous[Title/Abstract])) OR (Colitides, Mucous[Title/Abstract])) OR (Mucous Colitides[Title/Abstract])) OR (Mucous Colitis[Title/Abstract])	Guideline, in the last 5 years	("irritable bowel syndrome"[MeSH Terms] OR "irritable bowel syndromes"[Title/Abstract] OR "syndrome irritable bowel"[Title/Abstract] OR "syndromes irritable bowel"[Title/Abstract] OR "colon irritable"[Title/Abstract] OR "irritable colon"[Title/Abstract] OR "colitis mucous"[Title/Abstract] OR "colitides mucous"[Title/Abstract] OR "mucous colitides"[Title/Abstract] OR "mucous colitis"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	10

Appendix D. Irritable Bowel Syndrome Treatment Algorithm