Irritable Bowel Syndrome: An Evidence-Based Approach

Anita Wong, MD
UCLA Department of Family Medicine Grand Rounds
June 28, 2023

Disclosures

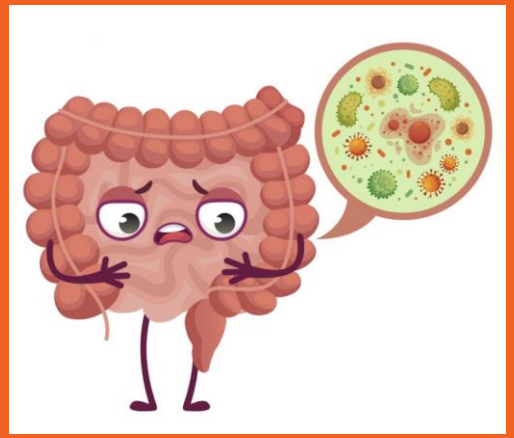
I have no disclosures to report.

1

Epidemiology of IBS

Why is knowing about IBS important?

- Prevalence in US is around 10-15%
- Direct medical costs related to IBS (not including medications) estimated to be $1.5-$10 billion a year
- IBS is the second-highest GI-related cause of work absenteeism in the US
- IBS accounts for 25% of all referrals to GI

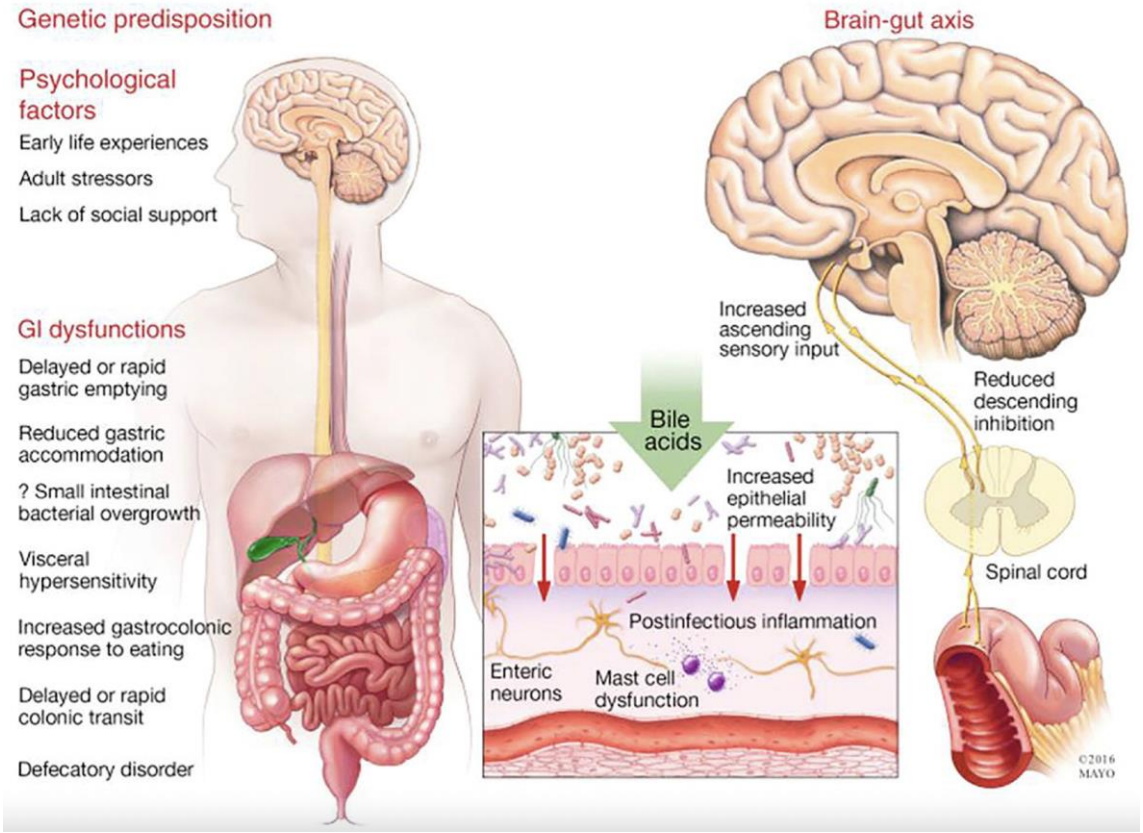


Epidemiology

- Females > males (14 % vs 9%)
- Younger > older (50+ yo)
- Associated conditions
  - Fibromyalgia
  - Chronic fatigue syndrome
  - GERD
  - Functional dyspepsia
  - Mon-cardiac chest pain
  - Psychiatric disorders: somatization, depression, anxiety

2

Pathophysiology of IBS



Common functional gastroenterological disorders associated with abdominal pain. Mayo Clin Proc. *2016;91(8):1122, with additional information from Camilleri M. Peripheral mechanisms in irritable bowel syndrome*. N Engl J Med. *2012;367(17):1626–1635*.

Multiple Factors Play a Role in IBS

Gastrointestinal Motility

Motor abnormalities detected including increased frequency of luminal contractions, prolonged transit time, and exaggerated motor response to meal ingestion.

Visceral Hypersensitivity

Increased stimulation of gut wall receptors transmit signals to afferent neural pathways to the dorsal horn of the spinal cord and then to the brain (brain-gut axis disorder).

Intestinal Inflammation

Alterations of immune cells and markers in the GI mucosa, including increased lymphocytes, increased mast cells, and elevated levels of proinflammatory cytokines.

Post-Infectious

6x increased risk of development of IBS following infectious enteritis, most commonly diarrhea symptoms.

Bacterial Overgrowth

Fecal microflora differ in individuals with IBS compared to healthy controls, and vary with predominant symptom.

Genetics

Modest contribution in twin studies with higher concordance rate for monozygotic twins (2-22%) compared to di-zygotic twins (1-9%).

Multiple Factors Play a Role in IBS

Psychosocial Dysfunction

- Patients with IBS report more lifetime and daily stressful events than control groups
- Anxiety, sleep problems and somatic symptoms are independent risk factors for developing IBS
- Corticotropin releasing factor (CRF) is a major mediator of the stress response, and IV administration increases abdominal pain and colonic mobility in IBS patients compared to controls

Food Sensitivity

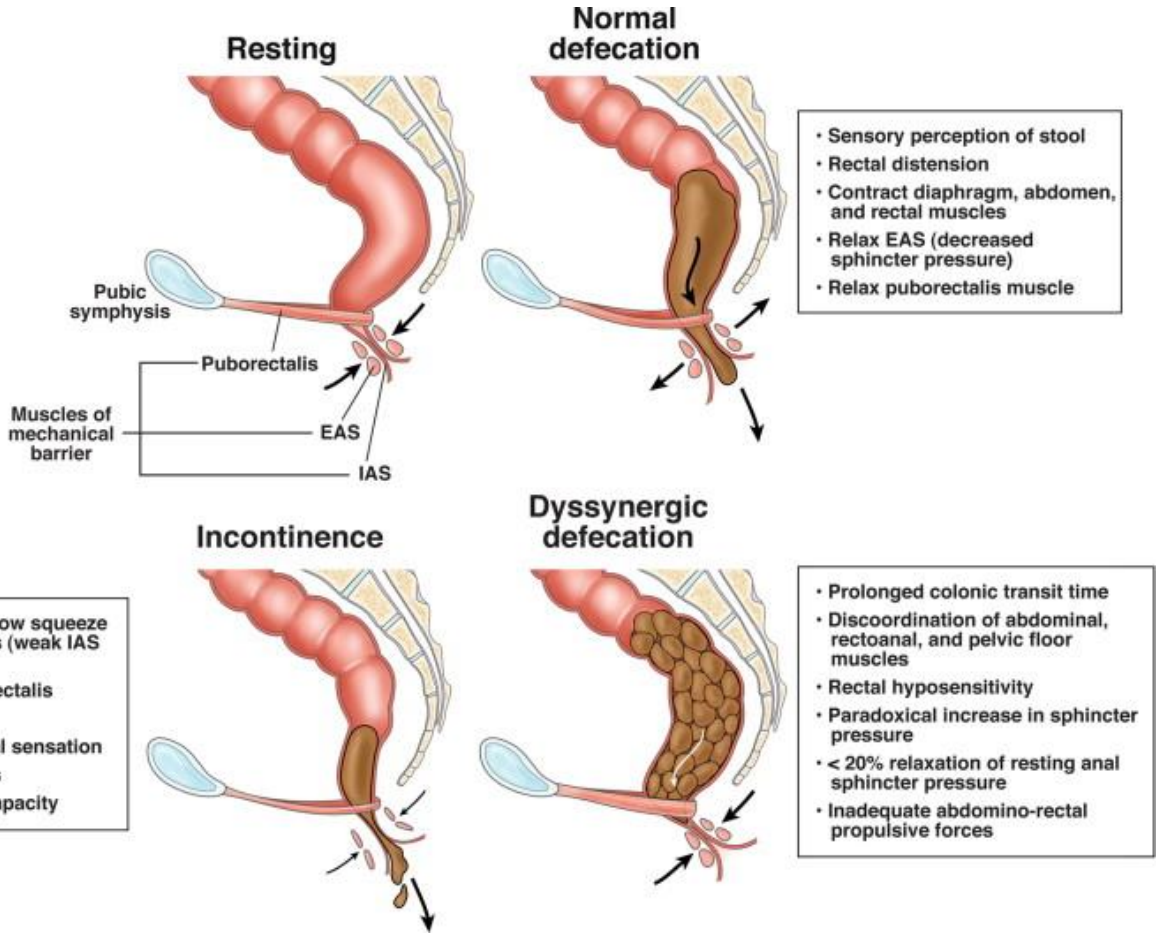
- Carbohydrate malabsorption: impaired absorption of fermentable carbohydrates leading to intestinal inflammation
- Gluten sensitivity: called non-celiac gluten sensitivity, celiac disease should be ruled out
- Food allergy: more positive food skin-prick tests (but challenge with foods did not cause symptoms)

3

Diagnosis of IBS

History and Physical

- Evaluate for symptoms concerning for organic disease
- Review medications that can cause diarrhea or constipation
- Family history of IBD, colorectal cancer, celiac disease
- Acute viral or bacterial gastroenteritis
- Exam usually benign
- Mild abdominal tenderness to palpation
- Digital rectal exam
  - Document if stool present and its consistency
  - Evaluate for dyssynergic defecation


Resting
Normal defecation
Pubic symphysis
Puborectalis
Muscles of mechanical barrier
EAS
IAS
• Sensory perception of stool
• Rectal distension
• Contract diaphragm, abdomen, and rectal muscles
• Relax EAS (decreased sphincter pressure)
• Relax puborectalis muscle
Incontinence
Dyssynergic defecation
• Low resting and/or low squeeze sphincter pressures (weak IAS and EAS)
• Weakness of puborectalis
• Neuropathy
• Altered rectal or anal sensation
• Diarrheal conditions
• Diminished rectal capacity
• Prolonged colonic transit time
• Discoordination of abdominal, rectoanal, and pelvic floor muscles
• Rectal hyposensitivity
• Paradoxical increase in sphincter pressure
• < 20% relaxation of resting anal sphincter pressure
• Inadequate abdomino-rectal propulsive forces

Medications associated with diarrhea

System	Type of Agent	Examples
Cardiovascular	Antiarrhythmics	Digoxin, procainamide, quinidine
	Anti-hypertensives	ACE-I, ARB, beta blockers, hydralazine, methyldopa
	Cholesterol-lowering agents	Clofibrate, gemfibrozil, statins
	Diuretics	Acetazolamide, ethacrynic acid, furosemide
Central nervous system	Anti-anxiety	Alprazolam, meprobamate
	Antiparkinsonian drugs	Levodopa
	Other agents	Anti-cholinergic agents, fluoxetine, lithium, tacrine
Endocrine	Oral hypoglycemic agents	Metformin
	Thyroid replacement	Synthroid
Gastrointestinal	Antacids	H2 receptor antagonists, magnesium containing antacids, PPIs
	Bile acids	Chenodeoxycholic acid, ursodeoxycholic acid
	Laxatives	Cathartics, lactulose, sorbitol
	IBD treatments	5-aminosalycilates (particularly olsalazine)

Medications associated with diarrhea

System	Type of Agent	Examples
Musculoskeletal	Gold salts	Auranofin
	NSAIDs	Ibuprofen, mefenamic acid, naproxen, phenylbutazone
	Gout	Colchicine
Other	Antibiotics	Amoxicillin, ampicillin, cephalosporins, clindamycin, neomycin, tetracycline
	Anti-neoplastic agents	Many
	Dietary	Alcohol, sugar substitutes (sorbitol)
	Vitamins	Magnesium, vitamin C

Medications associated with constipation

Type of Agent	Examples
Analgesics	Opiates
Anticholinergics	Antihistamines, antispasmodics, antidepressants, antipsychotics
Cation-containing agents	Iron supplements, aluminum (antacids, sucralfate), barium
Neurally active agents	Antihypertensives, ganglionic blockers, vinca alkaloids, calcium channel blockers, serotonin antagonists

Rome IV Criteria for IBS

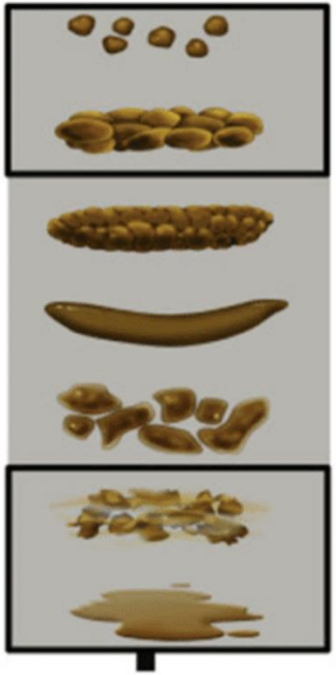
Recurrent abdominal pain on average at least 1 day/week in the last 3 months, started at least 6 months ago, and associated with two or more of the following:

1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (consistency) of stool

Lacy BE and Patel NK. Rome Criteria and a Diagnostic Approach to Irritable Bowel Syndrome. *J Clin Med*. 2017;6(11):99.

Bristol Stool Form Scale (BSFS)

A



Type 1	Separate hard lumps, like nuts (hard to pass)
Type 2	Sausage-shaped but lumpy
Type 3	Like a sausage but with cracks on the surface
Type 4	Like a sausage or snake, smooth and soft
Type 5	Soft blobs with clear-cut edges
Type 6	Fluffy pieces with ragged edges, a mushy stool
Type 7	Watery, no solid pieces, entirely liquid

Manning Criteria

- Pain relieved with defecation
- More frequent stools at onset of pain
- Looser stools at onset of pain
- Visible abdominal distention
- Passage of mucus
- Sensation of incomplete evacuation

*Sensitivity 67%, specificity 70% if 3 or more items are positive
*Mean score and overall frequency were higher than in non-ulcer dyspepsia or organic GI disease
*Pain-predominant IBS patients had significantly higher scores than painless IBS patients

Talley NJ et al. Diagnostic value of the Manning criteria in irritable bowel syndrome. *Gut*. 1990;31(1):77-81.

Laboratory Testing

- All patients:
  - CBC
  - Age-appropriate colorectal cancer screening
- Patients with constipation:
  - XR KUB to assess for stool accumulation
- Patients with diarrhea:
  - Fecal calprotectin
  - Bacterial stool tests
  - O&P testing
  - Serologic testing for celiac disease
  - CRP (if calprotectin cannot be checked)

* In patients who meet diagnostic criteria for IBS and have no alarm features, this limited diagnostic approach rules out organic disease in > 95% of patients.

Differential Diagnosis

- Diarrhea-predominant
  - Celiac disease
  - Microscopic colitis
  - Small intestinal bacterial overgrowth
  - Inflammatory bowel disease (Crohn's disease, ulcerative colitis)
  - Medications
  - Malignancy (GI, pelvic)
- Constipation-predominant
  - Dyssynergistic defecation
  - Slow colonic transit
  - Medications
  - Malignancy (GI, pelvic)
  - Constipation

Alarm Features

- Age of onset > 50
- Rectal bleeding o
- Nocturnal diarrhea
- Progressive abdominal pain
- Unexplained weight loss
- Lab abnormalities: iron d anemia, elevate calprotectin
- Family history of IBD, c ectal cancer, ovarian cancer
- Fever
- Jaundice
- Lymphadenopathy

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2013;11:956–962

A Positive Diagnostic Strategy Is Noninferior to a Strategy of Exclusion for Patients With Irritable Bowel Syndrome

LUISE M. BEGTRUP,*,‡ ANNE LINE ENGSBRO,§ JENS KJELDSEN,* PIA V. LARSEN,‡ OVE SCHAFFALITZKY DE MUCKADELL,* PETER BYTZER,§ and DORTE E. JARBØL‡

*Department of Gastroenterology, Odense University Hospital, Odense; ‡Research Unit of General Practice, Institute of Public Health, University of Southern Denmark, Odense; and §Department of Medicine, Køge Hospital, Køge, and Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark

BACKGROUND & AIMS: Guidelines recommend a positive strategy based on symptom criteria to diagnose patients with irritable bowel syndrome (IBS). We conducted a randomized noninferiority trial to determine whether a positive diagnostic strategy is noninferior to a strategy of exclusion, with regard to patients' health-related quality of life (HRQOL).

METHODS: We studied 302 patients (18–50 years old) from primary care who were suspected of having IBS and referred by general practitioners. Patients who fulfilled the Rome III criteria for IBS with no alarm signals were randomly assigned to groups assessed by a strategy of exclusion (analyses of blood, stool samples for intestinal parasites, and sigmoidoscopies with biopsies) or a positive strategy (analyses of blood cell count and C-reactive protein). Patients were followed for 1 year. The primary end point was difference in change of HRQOL from baseline to 1 year between groups (on the basis of the Short Form 36 health survey, physical component summary, and noninferiority margin of 3 points). Secondary outcomes were change in gastrointestinal symptoms, satisfaction with management, and use of resources. Findings of diagnostic misclassification were registered.

RESULTS: A positive strategy was noninferior to a strategy of exclusion (difference, 0.64; 95% confidence interval, −2.74 to 1.45). The positive diagnostic strategy had lower direct costs. Each approach had similar effects on symptoms, satisfaction, and subsequent use of health resources. No cases of inflammatory bowel disease, colorectal cancer, or celiac disease were found.

CONCLUSIONS: In diagnosing IBS in primary care, use of a positive diagnostic strategy is noninferior to using a strategy of exclusion with regard to the patients' HRQOL. Our findings support the current guideline recommendations. ClinicalTrials.gov, Number NCT00659763 and NCT01153295.

4

Treatment Modalities for IBS

ACG Clinical Guideline: Management of Irritable Bowel Syndrome

Brian E. Lacy, PhD, MD, FACG[1], Mark Pimentel, MD, FACG[2], Darren M. Brenner, MD, FACG[3], William D. Chey, MD, FACG[4], Laurie A. Keefer, PhD[5], Millie D. Long, MDMPH, FACG (GRADE Methodologist)[6] and Baha Moshiree, MD, MSc, FACG[7]

Irritable bowel syndrome (IBS) is a highly prevalent, chronic disorder that significantly reduces patients' quality of life. Advances in diagnostic testing and in therapeutic options for patients with IBS led to the development of this first-ever American College of Gastroenterology clinical guideline for the management of IBS using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. Twenty-five clinically important questions were assessed after a comprehensive literature search; 9 questions focused on diagnostic testing; 16 questions focused on therapeutic options. Consensus was obtained using a modified Delphi approach, and based on GRADE methodology, we endorse the following: We suggest that a positive diagnostic strategy as compared to a diagnostic strategy of exclusion be used to improve time to initiating appropriate therapy. We suggest that serologic testing be performed to rule out celiac disease in patients with IBS and diarrhea symptoms. We suggest that fecal calprotectin be checked in patients with suspected IBS and diarrhea symptoms to rule out inflammatory bowel disease. We recommend a limited trial of a low fermentable oligosaccharides, disacchardies, monosaccharides, polyols (FODMAP) diet in patients with IBS to improve global symptoms. We recommend the use of chloride channel activators and guanylate cyclase activators to treat global IBS with constipation symptoms. We recommend the use of rifaximin to treat global IBS with diarrhea symptoms. We suggest that gut-directed psychotherapy be used to treat global IBS symptoms. Additional statements and information regarding diagnostic strategies, specific drugs, doses, and duration of therapy can be found in the guideline.

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B755.

Am J Gastroenterol 2021;116:17–44. https://doi.org/10.14309/ajg.0000000000001036; published online December 14, 2020

Recommendation

We suggest that categorizing patients based on an accurate IBS subtype improves patient therapy.

Consensus recommendation; unable to assess using GRADE methodology.

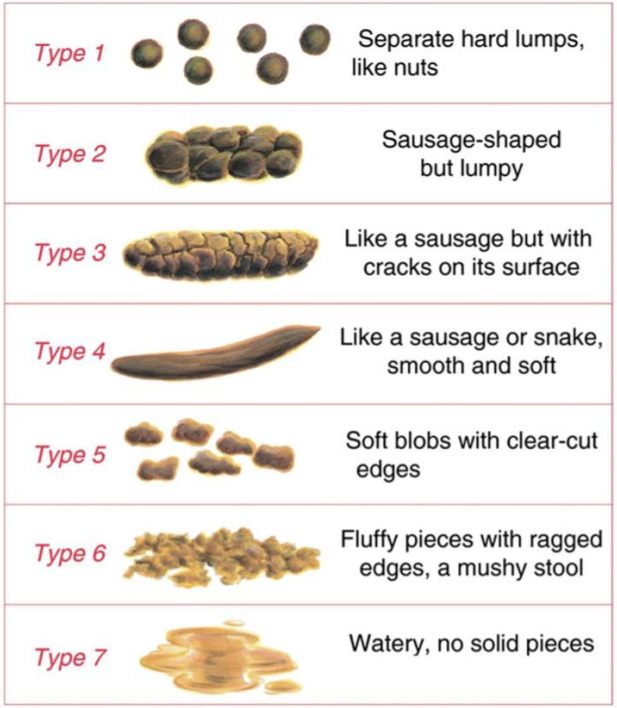
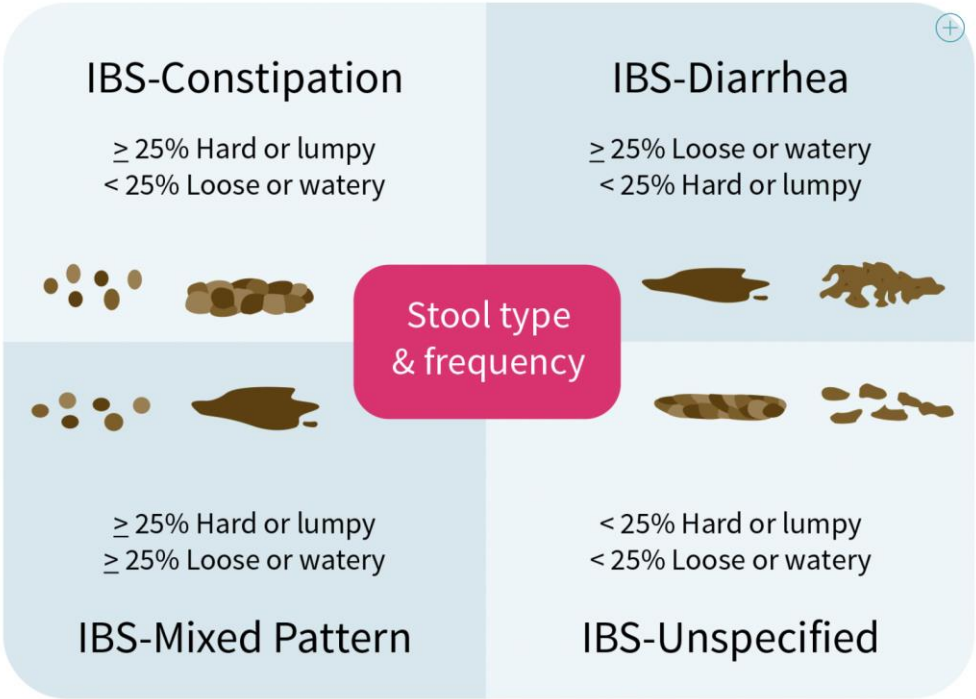


Figure 1. Bristol Stool Form Scale (English for the United States). Reprinted with permission from the Rome Foundation. ©2000 Rome Foundation. All Rights Reserved.

To accurately categorize a patient with IBS by subtype, we recommend the following:

1. Predominant stool consistency can be determined based on the Bristol Stool Form Scale (BSFS) (80) (Figure 1).
2. Determine patient's primary stool consistency only on the days s/he reports abnormal bowel movements. This determination should be made when patient is off of therapy(ies) that could affect bowel pattern. Daily diaries should be performed for 2 weeks for the most accurate assessment.
3. Once the pattern of stool consistency is determined, subtype decisions can be made according to the Rome IV criteria (4):
   a. IBS-C: >25% of bowel movements associated with BSFS 1 or 2 with BSFS 6 or 7 occurring less than 25%.
   b. IBS-D: >25% of bowel movements associated with BSFS 6 or 7 with less than 25% of bowel movements with BSFS 1 or 2.
   c. IBS-M: >25% of bowel movements associated with BSFS 1 or 2 and >25% of bowel movements associated with BSFS 6 or 7.
   d. IBS-U: cannot be determined.

IBS Subtypes



4a

Treatment Modalities for Global IBS

Recommendation

We recommend a limited trial of a low FODMAP diet in patients with IBS to improve global symptoms.

Conditional recommendation; very low quality of evidence.

Put simply, FODMAPs are a collection of short-chain carbohydrates (sugars) that aren't absorbed properly in the gut, which can trigger symptoms in people with IBS. FODMAPs are found naturally in many foods and food additives.

Fermentable

Process through which gut bacteria ferment undigested carbohydrate to produce gases.

Oligosaccharides

Fructans & GOS - found in foods such as wheat, rye, onions, garlic and legumes/pulses.

Disaccharides

Lactose - found in dairy products like milk, soft cheeses and yogurts.

Monosaccharides

Fructose - found in honey, apples, high fructose corn syrups, etc.

And

Polyols

Sorbitol and Mannitol - Found in some fruit and vegetables and used as artificial sweeteners.

HIGH FODMAP FOODS AND LOW FODMAP ALTERNATIVES

	HIGH FODMAP FOODS	LOW FODMAP ALTERNATIVES
Vegetables	Artichoke, asparagus, cauliflower, garlic, green peas, mushrooms, onion, sugar snap peas	Aubergine/eggplant, bean(green), bok choy, capsicum (bell pepper), carrot, cucumber, lettuce, potato, tomato, zucchini
Fruits	Apples, apple juice, cherries, dried fruit, mango, nectarines, peaches, pears, plums, watermelon	Cantaloupe, grapes, kiwi fruit (green), mandarin, orange, pineapple, strawberries
Dairy and alternatives	Cow's milk, custard, evaporated milk, ice cream, soy milk (made from whole soybeans), sweetened condensed milk, yoghurt	Almond milk, brie/camembert cheese, feta cheese, hard cheeses, lactose-free milk, soy milk (made from soy protein)
Protein sources	Most legumes/pulses, some marinated meats/poultry/seafood, some processed meats	Eggs, firm tofu, plain cooked meats/poultry/seafood, tempeh
Breads and cereal products	Wheat/rye/barley based breads, breakfast cereals, biscuits and snack products	Corn flakes, oats, quinoa flakes, quinoa/rice/corn pasta, rice cakes (plain), sourdough spelt bread, wheat/rye/barley free breads
Sugars/ sweeteners & confectionery	High fructose corn syrup, honey, sugar free confectionery	Dark chocolate, maple syrup, rice malt syrup, table sugar
Nuts and seeds	Cashews, pistachios	Macadamias, peanuts, pumpkin seeds, walnuts

Three-Step FODMAP Diet

STEP 1

Low FODMAP Diet

Follow a low FODMAP diet by swapping high FODMAP foods for low FODMAP alternatives. Aim is to induce symptom control.

STEP 2

FODMAP Reintroduction Diet

A low FODMAP diet continued. Food challenges (using foods high in only 1 FODMAP group) are used to determine which FODMAPs are tolerated, and which are not. Aim is to identify individual FODMAP sensitivities.

STEP 3

FODMAP Personalization Diet

Well tolerated FODMAPs are included, while poorly tolerated FODMAPs restricted, but only to a level that provides adequate symptom relief. Aim is establish a minimally restrictive, 'personalised FODMAP diet' for the long term.

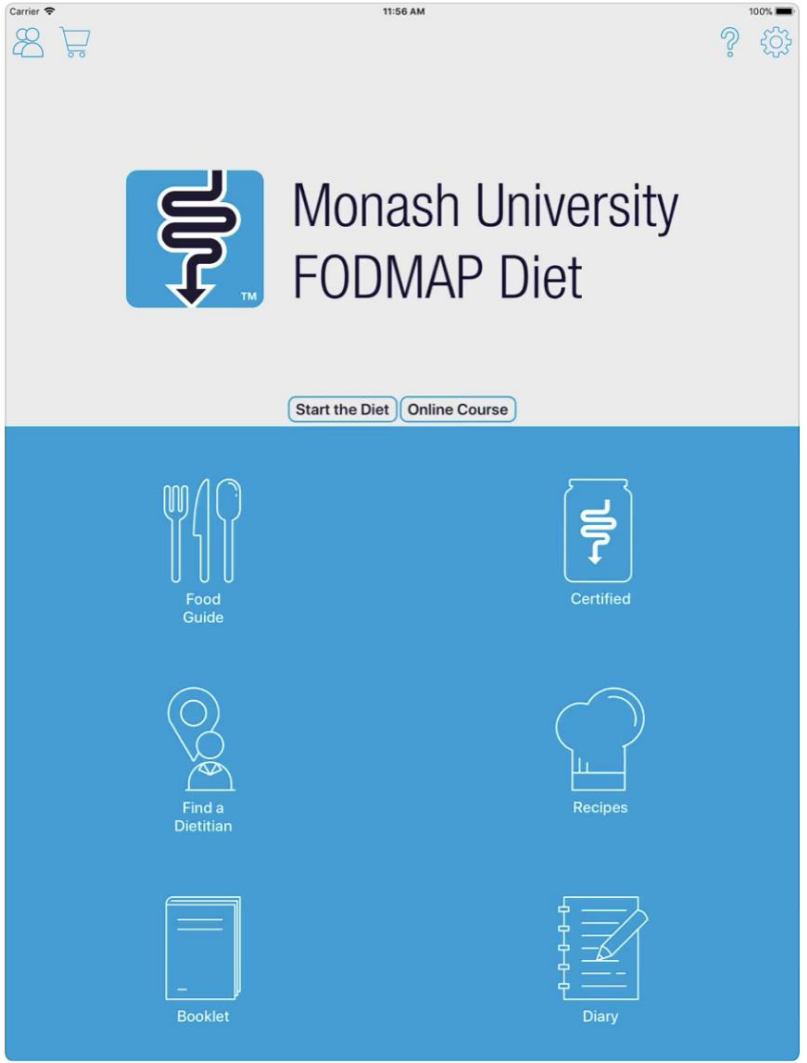
Monash University FODMAP diet

Medical

Designed for iPad

$7.99

* I do not make any money or benefit in any way from purchase of this app.



5:09 AM Wed Jun 5

100%

Guide

Fruit

- Avocado — 2.82oz 1.59oz 1.06oz
- Banana chips, dried — 1.06oz 1.20oz 1.41oz
- Banana, common (ripe) — 3.53oz 1.59oz 1.23oz
- Banana, common (unripe) — 3.53oz 3.88oz
- Banana, sugar (firm) — 3.95oz
- Banana, sugar (ripe) — 3.95oz 2.96oz 1.98oz
- Blackberry — 5.64oz 0.25oz 0.14oz
- Blueberry — 4.41oz 1.76oz 1.41oz
- Boysenberry — 0.85oz 0.42oz
- Breadfruit — 6.77oz
- Cantaloupe / Rockmelon — 5.29oz 4.23oz
- Carambola

Avocado

1 serve (½ whole avocado) — 2.82oz

Fructose	Lactose	Mannitol
Sorbitol	GOS	Fructan

This serving size contains high amounts of the Polyol-sorbitol and intake should be avoided if you malabsorb sorbitol.

*Please note that the 'green' traffic light rating system allows you to eat multiple serves of 'green' foods per meal. Nutritional guidelines recommend that on average per day you should eat at least 5 serves of vegetables and 2 serves of fruits.

½ serve (¼ whole avocado) — 1.59oz

Fructose	Lactose	Mannitol
Sorbitol	GOS	Fructan

This serving size contains moderate amounts of the Polyol-sorbitol and intake should be avoided if you malabsorb sorbitol.

5:10 AM Wed Jun 5

100%

Category

Main meals

- Vegetarian lasagne
- Rice paper rolls
- Fried rice
- Homemade margherita pizza
- Omelette wrap
- Tuna and sweet potato patties
- Homemade sushi rolls

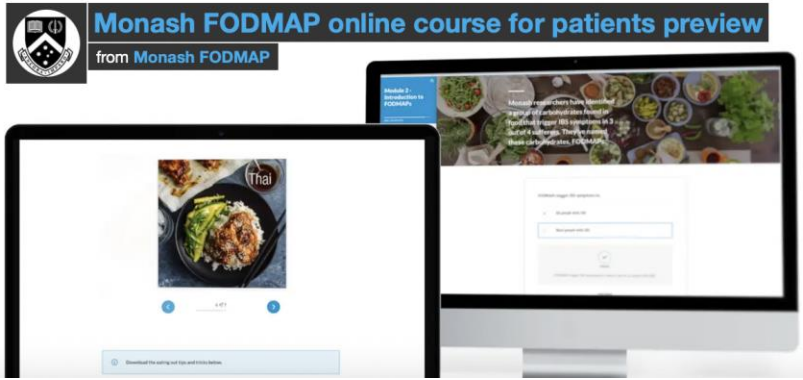
Vegetarian lasagne

Ingredients | Steps

1½ tablespoon garlic infused olive oil	0.79oz
2 medium zucchini (courgette)	12.35oz
1 medium red capsicum (bell pepper)	3.25oz
½ medium sweet potato	6.53oz
1 teaspoon dried oregano	0.07oz
1 handful baby spinach leaves	1.76oz
canned, diced tomatoes	17.64oz
1 cup low fat ricotta cheese	8.47oz
cottage cheese	5.29oz
¾ cup milk, low fat (lactose free if required)	6.81oz
6-8 lasagne sheets, gluten free	2.82oz

Online FODMAP and IBS training for patients

Learn how to manage your IBS using a FODMAP diet



Course fees (Introductory offer)

USD $29.99

AUD $46 (incl GST)

Course completion is due 12 months from time of registration and payment.

Low FODMAP diet A to Z

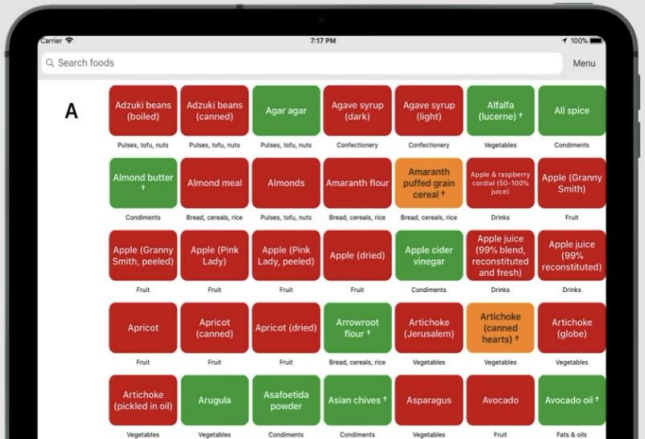
Food list for IBS sufferers

Designed for iPad. Not verified for macOS.

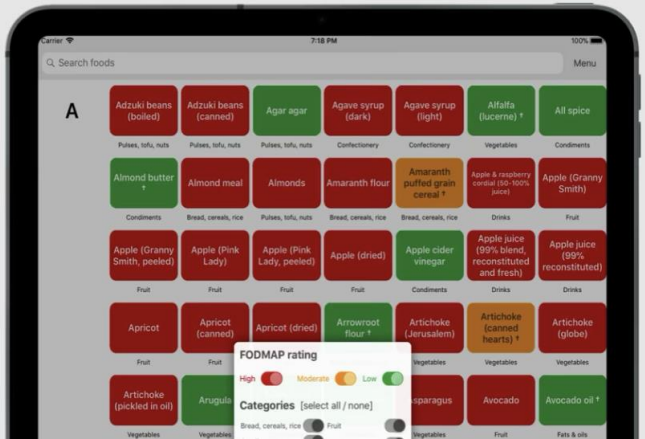
GET

AGE	CATEGORY	DEVELOPER	LANGUAGE
4+	Health & Fitness	Temeraire 1798 Ltd	EN
Years Old			English

Clear and simple food ratings



Search and filter the list to find foods fast



Meta-Analysis > Am J Gastroenterol. 2018 Sep;113(9):1290-1300.
doi: 10.1038/s41395-018-0195-4. Epub 2018 Jul 26.

A Systematic Review and Meta-Analysis Evaluating the Efficacy of a Gluten-Free Diet and a Low FODMAPs Diet in Treating Symptoms of Irritable Bowel Syndrome

Joanna Dionne [1], Alexander C Ford [1 1], Yuhong Yuan [1], William D Chey [1], Brian E Lacy [1], Yuri A Saito [1], Eamonn M M Quigley [1], Paul Moayyedi [1 1]

Affiliations + expand

PMID: 30046155 DOI: 10.1038/s41395-018-0195-4

Results: A total of 1726 citations were identified. After full-text screening a total of nine studies were eligible for the systematic review. There were two RCTs of a GFD, involving 111 participants. Both selected patients who responded to a GFD and then randomized them to continue the diet or have the diet "spiked" with gluten. A GFD was associated with reduced global symptoms compared with a control diet (RR = 0.42; 95% CI 0.11 to 1.55; I^2 = 88%), although this was not statistically significant. There were seven RCTs comparing a low FODMAP diet with various control interventions in 397 participants. A low FODMAP diet was associated with reduced global symptoms compared with control interventions (RR = 0.69; 95% CI 0.54 to 0.88; I^2 = 25%). The three RCTS that compared low FODMAP diet with rigorous control diets had the least heterogeneity between studies, but also the least magnitude of effect. The overall quality of the data was "very low" according to GRADE criteria.

Conclusions: There is insufficient evidence to recommend a GFD to reduce IBS symptoms. There is very low quality evidence that a low FODMAP diet is effective in reducing symptoms in IBS patients.

Recommendation

We suggest that soluble, but not insoluble, fiber be used to treat global IBS symptoms.

Strong recommendation; moderate quality of evidence.

Types of Fiber

Soluble fiber • Dissolves partially in water in large intestine and forms a gel • Psyllium, oat bran, barley, beans, ispaghula husk	Insoluble fiber • Does not dissolve in water • Physically fills up space in the stomach and intestines • Wheat bran, whole grains, some vegetables
Poorly fermentable fiber • Exert laxative effects • Increase stool water content to resist fermentation	Fermentable fiber • Lose water-holding capacity in the colon, producing gas

Evidence for Fiber

- Moayyedi et al. Systematic review and meta-analysis looking at 15 RCT involving 946 patients
  - 6 RCTs with 411 patients evaluated bran (insoluble, non-viscous, poorly fermentable fiber) and showed no significant benefit
  - 7 RCTs with 499 patients evaluated ispaghula husk (soluble, viscous, poorly fermentable fiber) and showed statistically significant benefit with NNT = 7
  - Adverse effects: 36% of tx vs 25.1% of placebo

Moayyedi R, Quigley EM, Lacy BE at al. The effect of fiber supplementation on irritable bowel syndrome: A systematic review and meta-analysis. *Am J Gastroenterol.* 2014;109:1367-74.

Fiber

- Soluble, viscous, poorly fermentable fiber may provide benefits in IBS, as the apparent lack of significant side effects makes fiber a reasonable first line therapy for IBS patients with symptoms
- The ability to improve stool viscosity and frequency logically argues for the use of fiber in patients with IBS-C, although the evidence base to support this contention is weak

Recommendation

We recommend against the use of antispasmodics currently available in the United States to treat global IBS symptoms.

Conditional recommendation; low quality of evidence.

Evidence for Anti-Spasmodics

- One of the most frequently used treatments for IBS
- Mechanism: relax intestinal smooth muscle to reduce GI motility
- Assessing efficacy is difficult because the class includes multiple agents with different mechanisms of action
- Historical recommendations supporting antispasmodics for treating global IBS symptoms have been predicated on systematic reviews and meta-analyses inclusive of all agents rather than looking at the evidence for individual agents
- Three commercially accessible anti-spasmodics in the US

Anti-Spasmodics: Dicyclomine (Bentyl)

- Page et al. Double-blind randomized study of 97 patients compared dicyclomine 40 mg daily to placebo daily for 2 weeks.
  - No standard definition of IBS or primary endpoint established
  - 84% tx group vs 54% placebo group reported improvement
  - 69% tx group vs 16% placebo group reported adverse effects
- Matts SGF. Double-blind randomized study of 96 patients compared dicyclomine 20 mg TID to placebo TID for 10 days.
  - No standard definition of IBS used
  - No statistical analysis used, just “subjective improvements” with dicyclomine compared with placebo
  - 33% tx group vs 4% placebo group reported adverse effects

Page JG, Dirnberger GM. Treatment of irritable bowel syndrome with Bentyl (dicyclomihne hydrochloride). *J Clin Gastroenterol.* 1981;3:153-6.
Matts SGF. An assessment of dicyclomine hydrochloride (‘Merbentyl’) in irritable colon syndrome. *Br J Clin Pract.* 1967;21:549-51.

Anti-Spasmodics: Hyoscyamine

- Available in multiple formulations: short-acting, long-acting, sublingual
- Single study in 1989 (Carling et al) of 25 patients randomized to hyoscyamine 0.2 mg vs placebo for 2 weeks
  - No standard definition of IBS used
  - Compared to peppermint oil instead of placebo
  - Comparable response to tx and "placebo"
  - High rate of adverse effects: 87% of tx vs 7% of placebo

Carling L, Svedberg LE, Hulten S. Short term treatment of irritable bowel syndrome: A placebo-controlled trial of peppermint oil against hyoscyamine. *OPMEAR*. 1989;34:55-7.

Anti-Spasmodics: Hyoscine (Scopolamine)

- Three trials performed outside of the US
- Ritchie et al. compared hyoscine, lorazepam, soluble fiber (ispaghula husk), and placebo in 8 permutable blocks with 12 subjects per block. Hyoscine fared no better than placebo over a 12-week period.
- Nigam P et al. compared hyoscine, amitriptyline with chlordiazepoxide, ispaghula, and placebo in 8 randomized blocks of 21 patients. At 12 weeks, individuals receiving only active hyoscine fared significantly better than those receiving placebo ($P < 0.02$).
- Schafer et al. randomized 712 individuals to hyoscine, hyoscine plus paracetamol, paracetamol alone, or placebo for 4 weeks. A "response" was achieved by 76% and 64% of individuals receiving hyoscine and placebo, respectively ($P < 0.05$), but the difference between hyoscine and paracetamol was only 4%. The most common AEs were dry mouth and blurred vision.

Ritchie JA, Truelove SC. Treatment of irritable bowel syndrome with lorazepam, hyoscine butylbromide, and ispaghula husk. *Br Med J.* 1979;1:376-8.
Nigam P, Kapoor KK, Rastog CK et al. Different therapeutic regimens in irritable bowel syndrome. *J Assoc Physicians India.* 1984;32:1041-4.
Schafer VE, Ewe K. The treatment of irritable colon. Efficacy and tolerance of buscopan plus, buscopan, paracetamol and placebo in ambulatory patient with irritable colon. *Fortschr Med.* 1990;108:488-92.

Anti-Spasmodics

- Data for anti-spasmodic use in IBS is old and of poor quality
- Side effects are common, especially in the elderly, although anecdotal evidence suggest that the agents are relatively safe
- Limited data supporting use in IBS

Recommendation

We suggest the use of peppermint to provide relief of global IBS symptoms.

Conditional recommendation; low quality of evidence.

Evidence for Peppermint Oil

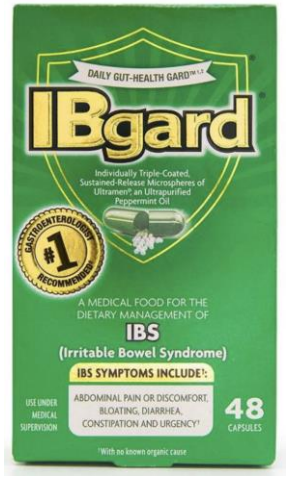
- Suggested mechanisms of action
  - L-menthol in peppermint oil blocks calcium channels in the gut leading to smooth muscle relaxation
  - Modulation of transient receptor potential voltage channels with effects on visceral sensation
  - Anti-microbial and anti-inflammatory effects
- Translational studies suggest it exerts effects on esophageal, gastric, small bowel, gallbladder and colonic function

Evidence for Peppermint Oil

- Alammar N et al. Meta-analysis evaluated 12 RCTs including 835 patients comparing daily use of peppermint oil to placebo
  - NNT for overall IBS symptoms was 3
  - NNT for improvement in abdominal pain was 4
  - Adverse effects: 9.3% tx vs 6.1% placebo
    - Most common was reflux (relaxation of lower esophageal sphincter), improves with enteric coated formulations
- Weerts et al. RCT of 190 patients with IBS defined by Rome IV criteria compared peppermint oil (182 mg) to placebo
  - Significant improvements in abdominal pain score ($P = 0.016$), discomfort ($P = 0.020$), and IBS severity ($P = 0.020$)

Alammar N, Wang L, Saberi B et al. The impact of peppermint oil on the irritable bowel syndrome: A meta-analysis of the pooled clinical data. *BMC Compliment Altern Med.* 2019;19:21.
Weerts ZZ, Masclee AAM, Witteman BJM et al. Efficacy and safety of peppermint oil in a randomized, double-blink trial of patients with IBS. *Gastroenterol.* 2020;158:123-36.

Peppermint Oil



- Peppermint oil has shown some benefit for overall symptoms and abdominal pain in patients with IBS
- Well-tolerated in available trials
- Only a small number of commercially available peppermint oil supplements have undergone rigorous testing of efficacy and safety

* I do not make any money or benefit in any way from purchase of this product.

Cash BD, Epstein MS, Shah SM. A novel delivery system of peppermint oil is an effective therapy for irritable bowel syndrome symptoms. *Dig Dis Sci 2016*. 61:560-71.

Recommendation

We suggest against probiotics for the treatment of global IBS symptoms.

Conditional recommendation; very low level of evidence.

Evidence for Probiotics

- Ford et al. Meta-analysis of 37 trials totaling 4403 patients
  - 21 studies involved probiotic combinations
    - Modest effect on abdominal pain but some studies showed worsened bloating symptoms
  - 16 involved single species studies
    - Studies evaluating Lactobacillus spp., Bifidobacterium spp., and Saccharomyces spp. did not seem to have a significant pooled benefit
  - Significant heterogeneity between studies

Ford AC, Harris LA, Lacy BE et al. Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. *Aliment Pharmacol Ther.* 2018;48:1044-60.

Probiotics

- Increased enthusiasm for probiotic use in IBS given the growing literature supporting the role of the microbiome
- Currently difficult to interpret existing data because of small studies the multiple types and strains of probiotics, the inconsistent benefits on individual symptoms, and the lack of rigorous trials based on US FDA endpoints, making meta-analysis difficult to perform and hard to interpret
- Future trials incorporating yet unidentified gut microbiome biomarkers or metabolomic markers may improve probiotic efficacy

Recommendation

We recommend that TCAs be used to treat global symptoms of IBS.
Strong recommendation; moderate quality of evidence.

Evidence for Tricyclic Antidepressants (TCAs)

- Mechanism of action
  - Act on norepinephrine and dopaminergic receptors to improve visceral and central pain
  - Anticholinergic effects at higher doses can slow GI transit and improve symptoms of diarrhea
  - Improve co-existing psychological distress
- Examples
  - Amitriptyline
  - Nortriptyline
  - Imipramine
  - Desipramine
  - Trimipramine
  - Doxepin

Evidence for Tricyclic Antidepressants (TCAs)

- Review of 12 RCTs with a total of 787 patients of all IBS subtypes compared TCA to placebo
- Of patients who received active therapy, 42.7% did not improve compared with 63.8% of those randomized to placebo who did not improve (NNT = 4.5)
- High rate of adverse effects (NNH = 9)
  - Dry mouth: 36% vs 15%
  - Insomnia: 24% vs 13%
  - Constipation: 23% vs 6%
  - Flushing: 23% vs 5%
  - Palpitations: 9% vs 2 %
  - Decreased appetite: 8% vs 1%
- No benefit with SSRIs

TCAs

- Data suggest that TCAs may improve global IBS symptoms, but there is not evidence to provide recommendations on a specific TCA
- Recommend starting on a low dose (i.e. amitriptyline 10 mg or desipramine 10 mg) with gradual dose titration upward to achieve therapeutic relief of symptoms while minimizing side effects
- Patients with IBS-D may respond better because of the anticholinergic properties of TCAs which may improve symptoms of urgency and diarrhea
- Caution should be directed toward potential side effects including dry mouth, dry eyes, urinary retention, constipation, and cardiac arrhythmias

4b

Treatment Modalities for IBS-C

Recommendation

We suggest against the use of PEG products to relieve global IBS symptoms in those with IBS-C.

Conditional recommendation; low quality of evidence

Evidence for Polyethylene Glycol (PEG)

- Inexpensive, widely available, non-prescription osmotic laxative
- FDA approved
- RCTs for chronic constipation show NNT of 3 for improvement in stool frequency and stool consistency
- Long-term (>6 month) safety in elderly patients without nutritional or electrolyte abnormalities
- Awad RA et al. RCT of 42 patients with IBS-C improved stool consistency but did not improve rectal pain or urgency to defecate.
- Chapman RW et al. RCT of 139 patients significantly improved number of spontaneous bowel movements but did not improve abdominal pain compared to placebo.

Awad RA, Camacho S. A randomized, double-blind, placebo-controlled trial of polyethylene glycol effects on fasting and postprandial rectal sensitivity and symptoms in hypersensitive constipation-predominant irritable bowel syndrome. *Colorectal Dis.* 2010;12:1131-8.
Chapman RW, Stanghellini V, Geraint M, et al. Randomized clinical trial: marcrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. *Am J Gastroenterol.* 2013;108:1508-15.

In summary, despite the long-term safety and efficacy of PEG for the treatment of chronic constipation in even the most vulnerable subjects (elderly and children), there is no evidence that PEG alleviates abdominal pain and thus global symptoms in patients with IBS-C. We therefore recommend against use of PEG **alone** for the treatment of global IBS-C symptoms, although we recognize that clinicians may use PEG as first-line treatment of constipation in IBS, given its low cost and availability.

Recommendation

We recommend the use of chloride channel activators to treat global IBS-C symptoms.

Strong recommendation; moderate quality of evidence.

Evidence for Chloride Channel Activators

- Lubiprostone
  - FDA approval
    - Treatment of chronic idiopathic constipation in adults
    - Treatment of IBS-C in women > 18 yo
  - Dose: 8 micrograms BID
  - Mechanism of Action
    - Locally acting prostaglandin E1 analogue with high affinity to type-2 chloride channels in apical membranes of intestinal epithelial cells
    - Stimulation of receptors increases intestinal secretion and peristalsis (secretagogue)
    - Animal studies suggest increased intestinal permeability helps restore barrier function

Evidence for Chloride Channel Activators

- Drossman et al. Meta-analysis of 3 RCTs of 1171 patients comparing lubiprostone to placebo
  - Improvement in overall symptoms was achieved by 23.8% with lubiprostone vs 12.6% with placebo (NNT 12.5)
  - Significant improvements in abdominal pain/discomfort, bloating, straining, stool frequency, and consistency
  - Separation between groups did not reach statistical significance until month 2 but was maintained throughout month 3
  - Adverse effects
    - Diarrhea: 6-14%
    - Nausea: 8-19%
    - Discontinuation rate low: 1.2% vs 0.7% placebo

Drossman DA, Chey WD, Johanson JF et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome- results of two randomized, placebo-controlled studies. *Aliment Pharmacol Ther*. 2009;29:329-41.

Chloride Channel Activators

- Lubiprostone 8 micrograms twice daily seems effective for relieving global and individual symptoms in patients with IBS- C
- Although there may be a delay in initial response, improvement in global symptoms is maintained or increases over time
- Most common AEs are mild
  - Nausea: 8-19%, may be reduced by consuming lubiprostone with meals
  - Diarrhea: 6-14%
  - Low discontinuation rate: 1.2%

Recommendation

We recommend the use of guanylate cyclase activators to treat global IBS-C symptoms.

Strong recommendation; high quality of evidence.

Evidence for Guanylate Cyclase -C Agonists

- Mechanism of action
  - Activates GC-C receptors in the apical membranes of intestinal epithelial cells, which increase intestinal fluid secretion and peristalsis (secretagogue)
  - Decreases activation of visceral nociceptive neurons
- Two US FDA approved agents for IBS-C
  - Linaclotide 290 micrograms daily
  - Plecanatide 3 mg daily

Evidence for Guanylate Cyclase -C Agonists

- Linaclotide: double-blind randomized phase IIb/III trials of 802 patients compared to placebo
  - After 12 weeks of therapy, 2/3 of patients who received linaclotide endorsed subjective improvement in abdominal pain, stool frequency and global IBS symptoms (NNT= 6)
  - Adverse effects: diarrhea in 20% vs 3% placebo, 5% discontinuation rate
- Plecanatide: double-blind randomized phase IIb/III trials of 728 patients compared to placebo
  - After 12 weeks of therapy, 26% of patients endorsed subjective improvement in global IBS symptoms (NNT = 9)
  - Adverse effects: diarrhea in 4.3% vs 1.2% placebo

Shad ED, Kim HM, Schoenfeld P. Efficacy and tolerability of guanylate cyclase-c agonists for irritable bowel syndrome with constipation and chronic idiopathic constipation: a systematic review and meta-analysis. *Am J Gastroenterol.* 2018;113:329-38.

Guanylate Cyclase-C Agonists

- GC-C agonists seem effective for relief of overall and individual symptoms of IBS-C
  - Linaclotide 290 micrograms daily
  - Plecanatide 3 mg daily
- Quick response and maintained over time
- Most common side effect is diarrhea, but discontinuation rates are low

Recommendation

We suggest that the 5-HT_4 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.

Conditional recommendation; low quality of evidence.

*Has since been withdrawn from US market due to cardiovascular risks

4c

Treatment Modalities for IBS-D

Recommendation

We recommend the use of rifaximin to treat global IBS-D symptoms.
Strong recommendation; moderate level of evidence.

Evidence for Rifaximin

- Mechanism of action
  - Non-absorbed antibiotic used to treat the abnormal microbiome in patients with IBS-D
- RCT of rifaximin 550 mg TID x 2 weeks vs placebo
  - 40.8% of patients had improvement in abdominal pain and stool consistency vs 31.7% with placebo
  - NNT = 9, NNH = 8971
  - No significant disruption of microbiome
  - Rare development of C diff colitis
  - More likely to respond if patients have a positive breath test (56% vs 25%) suggesting bacterial overgrowth

Lembo A, Pimentel M, Rao SS et al. Repeat treatment with rifaximin is safe and effective in patients with diarrhea predominant irritable bowel syndrome. *Gastroenterol.* 2016;151:1113-21.

Rifaximin

- Rifaximin is FDA-approved for treatment of IBS-D
  - 550 mg TID
  - Treat for two weeks
  - If symptoms improve, but patient relapses, can repeat treatment for up to two more courses
- Consider hydrogen breath test before treatment as patients who are positive are more likely to respond

Recommendation

We 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.

Evidence for 5-HT_3 Antagonists

- Alosetron 0.5 – 1 mg BID
- Mechanism of action
  - 5-HT_3 antagonist that blocks serotonin receptors and leads to slowing of intestinal transit and improvement of diarrhea
- Two RCTs with global improvement rates of 12.2 – 32% compared to placebo (only studied in women)
- Real world, open label prospective observational analysis with response rate of 45%

Zheng Y, Yu T, Tang Y et al. Efficacy and safety of 5-hydroxytryptamine 3 receptor antagonists in irritable bowel syndrome: a systematic review and meta-analysis of randomized controlled trials. *PLoS One*. 2017;12:e0172846.

Evidence for 5-HT_3 Antagonists

- Safety concerns
  - Post-marketing reports of increased rates of ischemic colitis, complicated constipation (obstruction or perforation) and death
  - Follow up meta-analysis with NNH = 10
    - Ischemic colitis: 1.03 cases/1,000 pt-years of exposure
    - Complicated constipation: 0.25 cases/1,000 pt-years
- Alosetron was reintroduced under a risk evaluation and mitigation strategy (REMS) in 2002

5-HT_3 Antagonists

- Alosetron is FDA-approved for women with IBS-D experiencing chronic (> 6 months), severe symptoms who previously lacked response to traditional therapies
  - Dose: 0.5-1 mg BID
  - Need to counsel on risks of ischemic colitis, complicated constipation
- Other studies looking at ondansetron (TRITON trial, international phase III trial)

Recommendation

We suggest that mixed opioid agonists/antagonists be used to treat global IBS-D symptoms.

Conditional recommendation; moderate quality of evidence.

Evidence for Mixed Opioid Agonists-Antagonists

- Eluxadoline
  - Peripherally acting, mixed mu- and kappa- opioid receptor agonist/delta-opioid receptor antagonist
  - Dose: 100 mg BID, 75 mg BID in mild to moderate hepatic impairment
  - Two RTCs showed improvement in abdominal pain and diarrhea with 100 mg and 75 mg doses compared to placebo (26.7% and 31.0% vs 19.5%)
    - NNT = 10 with 100 mg dose
    - NNT = 14 with 75 mg dose

Lembo AJ, Lacy BE, Zyckerman MJ et al. Eluxadoline for irritable bowel syndrome with diarrhea. *N Engl J Med.* 2016;374:242-53.

Evidence for Mixed Opioid Agonists-Antagonists

- Adverse effects
  - Constipation: 8% vs 2.5% with placebo (usually in first 3 months of treatment)
  - Nausea: 7.7% vs 5% with placebo
  - Sphincter of Oddi spasm: 0.5% of patients (all without gallbladder)
  - NNH: 25 (75 mg BID dose), 23 (100 mg BID dose)

Lembo AJ, Lacy BE, Zyckerman MJ et al. Eluxadoline for irritable bowel syndrome with diarrhea. *N Engl J Med.* 2016;374:242-53.

Mixed Opioid Agonists-Antagonists

- Eluxadoline improves symptoms in patients with IBS-D
  - Usual dose: 100 mg BID
  - Hepatic impairment: 75 mg BID
- Contraindications
  - History of pancreatitis
  - Sphincter of Oddi dysfunction

4d

Behavioral Treatment Modalities

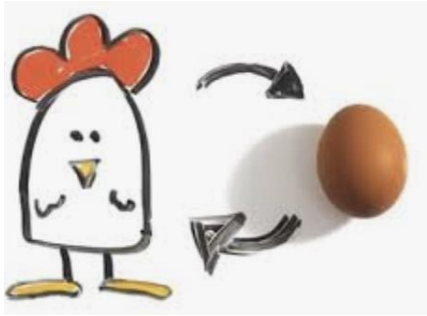
Recommendation

We suggest that gut-directed psychotherapies be used to treat global IBS symptoms.

Conditional recommendations; very low quality of evidence.

Evidence for Psychotherapy

- Gut-directed psychotherapies (GDPs)
  - Cognitive-behavioral therapy (CBT-GI)
  - Gut-directed hypnotherapy (GDH)
- Improve IBS symptom severity by targeting the cognitive and affective factors known to drive symptom experience
  - Fear of symptoms
  - Attentional bias/hypervigilance
  - Somatization
  - Stress sensitivity



Evidence for Psychotherapy

- Wide range of skills-based techniques
  - Relaxation training
  - Cognitive reframing of unhelpful thoughts
  - Decreasing helplessness
  - Behavioral experimentation around avoidance of symptoms or settings in which they occur
  - Techniques that alter pain perception
- Well tested as adjunct to medical therapies, but no RCTs to compare stand-alone GDPs against pharmacotherapy
- Less effective in patients with co-morbid mental health conditions

Gut-Directed Psychotherapy

- We recommend use of GDPs in conjunction with other IBS therapies who are emotionally stable but who exhibit cognitive-affective drivers of IBS symptoms despite low quality evidence
  - Low-risk: no serious side effects or negative outcomes reported in studies
  - There are long-term benefits of therapies even after they are discontinued
  - Can be used in all IBS sub-types, and can address patients with IBS-M or IBS-U for whom fewer pharmacological treatments are available

Summary

- IBS is a chronic, multifactorial, functional GI disorder that affects 10-15% of the US population
- If a patient does not have red flag symptoms, a limited workup is usually enough to rule out other causes of symptoms
- Identifying the IBS subtype is helpful to guide treatment
- A multi-modal and multi-disciplinary approach is most effective at improving symptoms of IBS

References

- Wilkinson JM and Gill MC. Irritable bowel syndrome: questions and answers for effective care. Am Fam Physician. 2021 Jun 15;103(12):727-736.
- Lacy BE et al. ACG clinical guideline: management of irritable bowel syndrome. Am J Gastroenterol. 2021;116:17-44.
- Camilleri M. Peripheral mechanisms in irritable bowel syndrome. N Engl J Med. 2012;367(17):1626–1635.
- Rao SSC. Advances in diagnostic assessment of fecal incontinence and dyssynergic defecation. *Clinical Gastroent and Hepatology*. 2010 Jun 28;8:910-919.
- El-Serag HB, Pilgrim P, Schoenfeld P. Systemic review: natural history of irritable bowel syndrome. *Aliment Pharmacol Ther*. 2004;19(8):861.
- Begtrup LM, Engsbro AL, Kjeldsen J et al. A positive diagnostic strategy is noninferior to a strategy of exclusion for patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol*, 2013;11:956-62.
- Dionne J, Ford AC, Yuan Y et al. A systematic review and meta-analysis evaluating the efficacy of a gluten free diet and a low FODMAP diet in treating symptoms of IBS. *Am J Gastroenterol*. 2018;113:1290-300.
- Awad RA, Camacho S. A randomized, double-blind, placebo-controlled trial of polyethylene glycol effects on fasting and postprandial rectal sensitivity and symptoms in hypersensitive constipation-predominant irritable bowel syndrome. *Colorectal Dis*. 2010;12:1131-8.
- Chapman RW, Stanghellini V, Geraint M, et al. Randomized clinical trial: marcrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. *Am J Gastroenterol*. 2013;108:1508-15.

References

- Page JG, Dirnberger GM. Treatment of irritable bowel syndrome with Bentyl (dicyclomihne hydrochloride). *J Clin Gastroenterol*. 1981;3:153-6.
- Matts SGF. An assessment of dicyclomine hydrochloride ('Merbentyl') in irritable colon syndrome. *Br J Clin Pract.* 1967;21:549-51.
- Carling L, Svedberg LE, Hulten S. Short term treatment of irritable bowel syndrome: A placebo-controlled trial of peppermint oil against hyoscyamine. *OPMEAR*. 1989;34:55-7.
- Ritchie JA, Truelove SC. Treatment of irritable bowel syndrome with lorazepam, hyoscine butylbromide, and ispaghula husk. *Br Med J*. 1979;1:376-8.
- Nigam P, Kapoor KK, Rastog CK et al. Different therapeutic regimens in irritable bowel syndrome. *J Assoc Physicians India*. 1984;32:1041-4.
- Schafer VE, Ewe K. The treatment of irritable colon. Efficacy and tolerance of buscopan plus, buscopan, paracetamol and placebo in ambulatory patient with irritable colon. *Fortschr Med*. 1990;108:488-92.
- Alammar N, Wang L, Saberi B et al. The impact of peppermint oil on the irritable bowel syndrome: A meta-analysis of the pooled clinical data. *BMC Compliment Altern Med.* 2019;19:21.
- Weerts ZZ, Masclee AAM, Witteman BJM et al. Efficacy and safety of peppermint oil in a randomized, double-blink trial of patients with IBS. *Gastroenterol*. 2020;158:123-36.
- Cash BD, Epstein MS, Shah SM. A novel delivery system of peppermint oil is an effective therapy for irritable bowel syndrome symptoms. *Dig Dis Sci 2016*. 61:560-71.

References

- Moayyedi R, Quigley EM, Lacy BE at al. The effect of fiber supplementation on irritable bowel syndrome: A systematic review and meta-analysis. *Am J Gastroenterol*. 2014;109:1367-74.
- Ford AC, Harris LA, Lacy BE et al. Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. *Aliment Pharmacol Ther*. 2018;48:1044-60.
- Drossman DA, Chey WD, Johanson JF et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome- results of two randomized, placebo-controlled studies. *Aliment Pharmacol Ther*. 2009;29:329-41.
- Shad ED, Kim HM, Schoenfeld P. Efficacy and tolerability of guanylate cyclase-c agonists for irritable bowel syndrome with constipation and chronic idiopathic constipation: a systematic review and meta-analysis. *Am J Gastroenterol*. 2018;113:329-38.
- Ford AC, Brandt LJ, Young C et al. Efficacy of 5-HT_3 antagonists and 5-HT_4 agonists in irritable bowel syndrome: systematic review and meta-analysis. *Am J Gastroenterol*. 2009;104:1831-43.
- Lembo A, Pimentel M, Rao SS et al. Repeat treatment with rifaximin is safe and effective in patients with diarrhea predominant irritable bowel syndrome. *Gastroenterol*. 2016;151:1113-21.
- Zheng Y, Yu T, Tang Y et al. Efficacy and safety of 5-hydroxytryptamine 3 receptor antagonists in irritable bowel syndrome: a systematic review and meta-analysis of randomized controlled trials. *PLoS One*. 2017;12:e0172846.
- Lembo AJ, Lacy BE, Zyckerman MJ et al. Eluxadoline for irritable bowel syndrome with diarrhea. *N Engl J Med*. 2016;374:242-53.

Questions?

"Looks like the doctor confirmed my diagnosis. It's not just your bowel. Everything about you is irritable."