



Medical Education for Practical Application

Recognition of Diarrhea-Predominant Irritable Bowel Syndrome (IBS-D): Advancing Accurate Diagnosis and Appropriate Treatment



Sponsored by Integrity Continuing Education, Inc.

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Faculty Disclosures

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Learning Objectives

- Recognize the significant and pervasive impact of irritable bowel syndrome (IBS) on patients, families, and caregivers
- Utilize evidence-based guidelines and available diagnostic tools to facilitate the timely and accurate diagnosis of IBS in patients with diarrhea
- Evaluate the efficacy and safety of newer treatments for irritable bowel syndrome with diarrhea (IBS-D)



Disease Overview

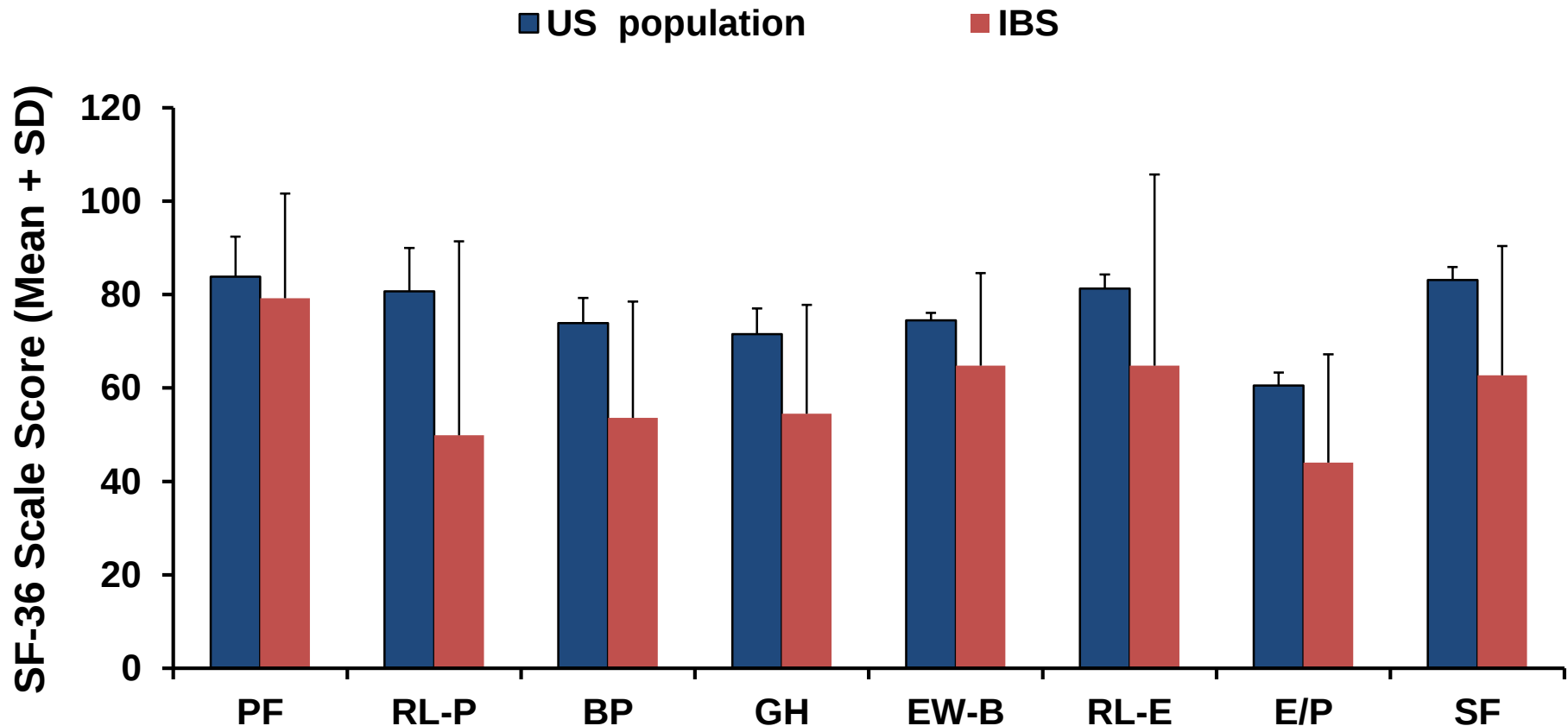
Overview of IBS

- IBS is the most frequently diagnosed functional GI disorder in primary and secondary care practices
- Affects ~15% - 20% of global populations
- Characterized by abdominal discomfort or pain accompanied by altered bowel function presenting as constipation (IBS-C), diarrhea (IBS-D), or both (IBS-M) in the absence of structural or biochemical abnormalities
- Associated with high medical costs, frequent doctor visits, missed workdays, and an overall detrimental impact on HRQOL

GI, gastrointestinal; HRQOL, health-related quality of life

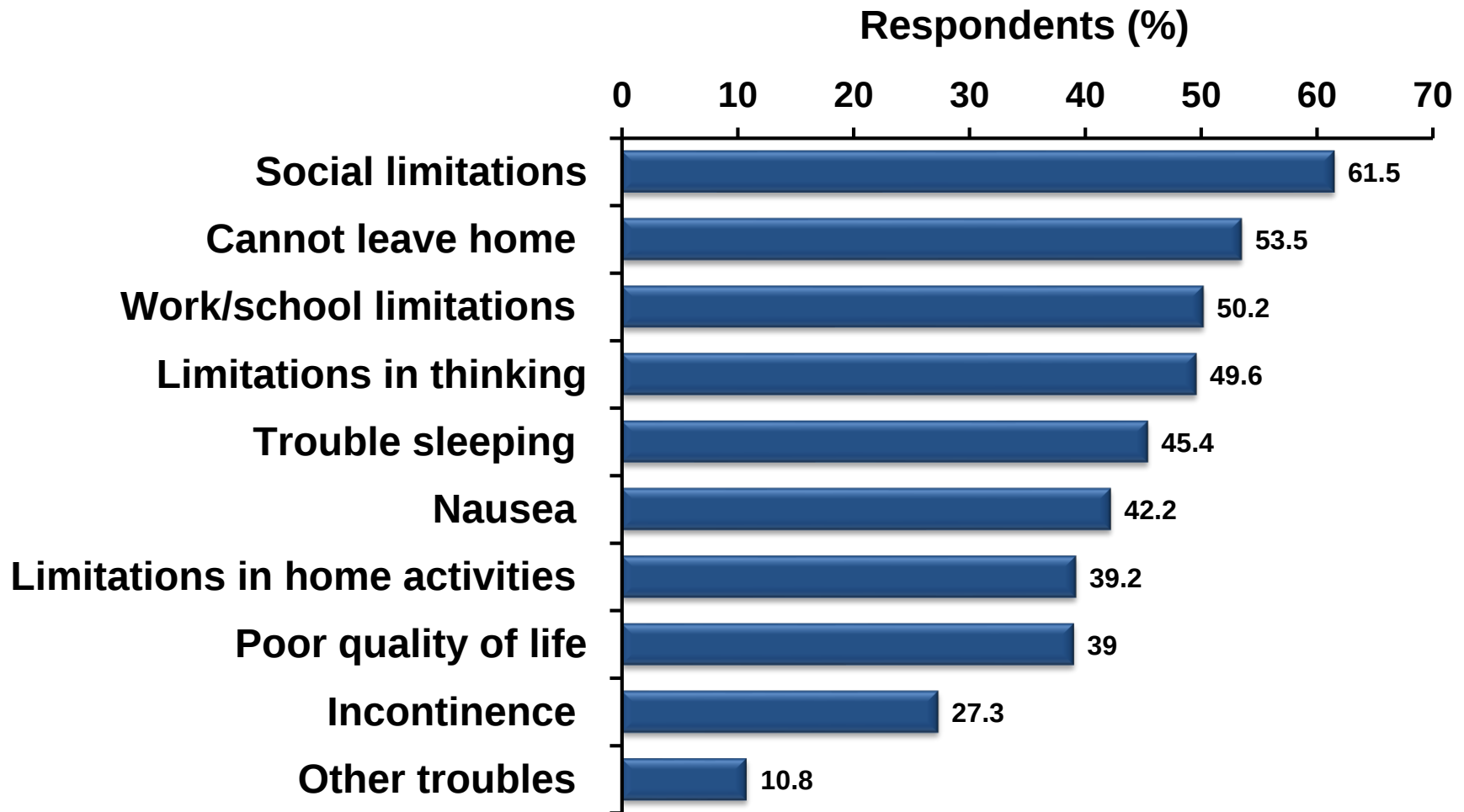
Lacy BE *International Journal of General Medicine*. 2016;9:7-17.

QOL is Significantly Worse for Patients with IBS vs the General US Population



SF-36, 36-Item Short Form Health Survey; PF, physical functioning; RL-P, role limitations-physical; BP, bodily pain; GH, general health; EW-B, emotional well-being; RL-E, role limitations-emotional; E/F, energy/fatigue; SF, social functioning

Patient-identified Factors that Contribute to Disease Burden



IBS-D is Associated with Lower Disease-Specific QOL vs IBS-C

IBS-QOL subscale	IBS-C (n = 54)	IBS-D (n = 56)	IBS-M (n = 121)	P-value
Interference with activity	82.3	59.6	61.6	< .001
Social reaction	80	59.6	61.6	.0082
Food Avoidance	61.1	45	47.2	.0203
Relationships	84.7	75.4	73.3	.0304
Dysphoria	69.2	57.1	58	.06
Health worry	64.3	60.9	57.3	.28
Sexual	73.9	74.6	68.8	0.5
Body Image	69.2	66	64.9	.631
Total	74.5	61.6	63	.0105

Pathogenesis of IBS

EXTRINSIC FACTORS

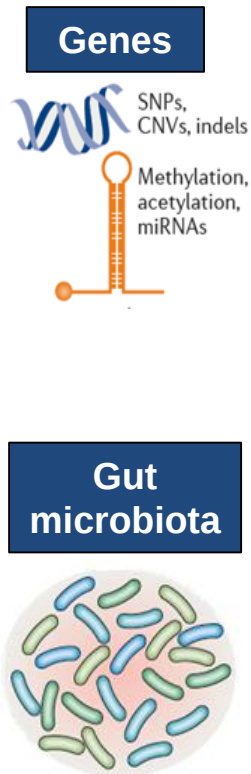


Pathogenesis of IBS

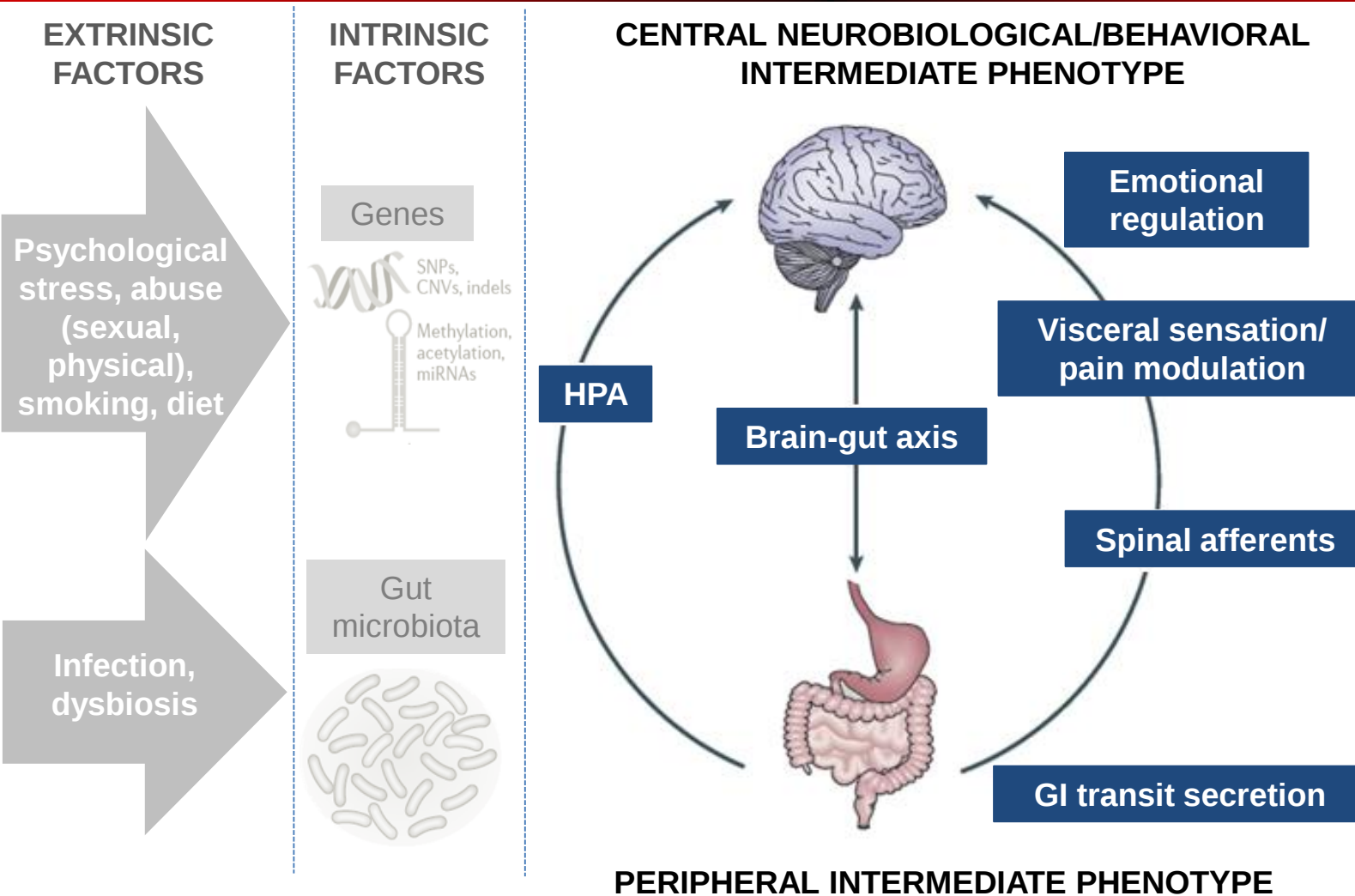
EXTRINSIC FACTORS



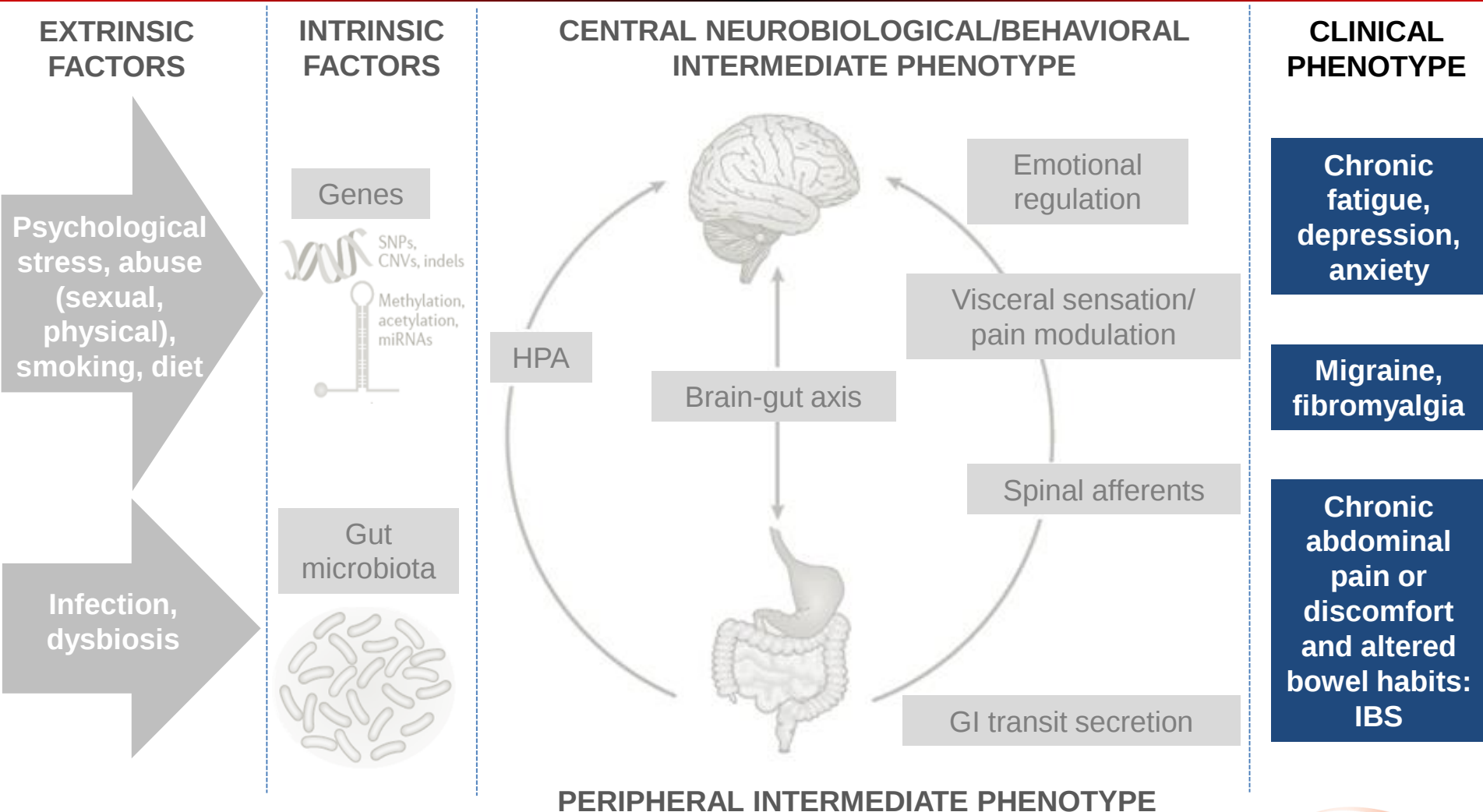
INTRINSIC FACTORS



Pathogenesis of IBS



Pathogenesis of IBS



HPA, hypothalamo-pituitary-adrenocortical [system].

Adapted from: Gazouli M, et al. *Nat Rev Gastroenterol Hepatol*. 2016;13(2):77-87.

Comorbidities Associated with IBS

Psychiatric Disorders

Anxiety, major depression, somatization

Somatic Pain Syndromes

Chronic fatigue syndrome, chronic pelvic pain, fibromyalgia

GI Disorders

GERD, dyspepsia

- 91% of patients with IBS reported ≥ 1 comorbidity
- Average number reported was 5 (1 mental, 4 physical)
- **Anxiety, depression, back pain, agoraphobia, tension headache, insomnia** were associated with greater illness and symptom burden



Screening and Diagnosis



Case Study #1: 40-year-old Woman

■ Clinical presentation

- Recurrent abdominal pain and periods of loose stools (symptoms present since patient's early 20's)
- Increasing in frequency and severity of attacks over the past 6 months
- Stools are frequently watery (occasionally with mucus, but without blood)
- Bowel movements 4 to 7 times per day and not awakening her
- Abdominal pain
 - Associated with bloating and gas
 - Exacerbated by eating
 - Relieved with defecation
- Weight loss of 9 lb over the past 3 to 4 months



Case Study #1: Physical Exam

- **Vital signs**
 - HR: 97 bpm
 - RR: 18 breaths/min
 - BP: 126/82 mm Hg
- **CV and pulmonary exam:**
 - Normal
- **Abdominal exam:**
 - Abdomen is flat
 - Bowel sounds are normal
 - Tympany in the upper-left quadrant
 - No organomegaly
 - Mild generalized tenderness



Case Study Discussion

- Individual symptoms have limited accuracy
- Alarm features are crucial for guidance
- Role of testing
- Recommended diagnostic tests

Diagnosis of IBS

Rome IV Criteria

1. Symptom onset ≥ 6 months prior to diagnosis
2. Recurrent abdominal pain, on average, ≥ 1 day/week in the last 3 months with ≥ 2 of the following:
 - Related to defecation
 - Associated with a change in stool frequency
 - Associated with a change in stool form (appearance)

Bristol Stool Form Scale

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

Subtyping IBS by Predominant Stool Pattern

IBS Subtype	Bowel Movements	
	Hard or Lumpy Stool Frequency	Loose or Watery Stool Frequency
IBS-C	≥25%	<25%
IBS-D	<25%	≥25%
IBS-M	≥25%	≥25%

ACG Guideline Recommendations for Diagnostic Testing*

Routine diagnostic testing	NOT recommended for patients with typical symptoms and no alarm features
Serologic screening for celiac sprue	Recommended for patients with IBS-D and IBS-M
Lactose breath testing	Recommended if lactose maldigestion persists despite dietary modification
Breath testing for SIBO	Insufficient data to recommend
Routine colonic imaging	NOT recommended for patients < 50 years of age with typical IBS symptoms and no alarm features
Colonoscopic imaging	Recommended for IBS patients with alarm features and those > 50 years of age
Random biopsies	Consider to rule out microscopic colitis if colonoscopy is performed

*CBC, serum chemistries, thyroid function studies, stool for ova and parasites, abdominal imaging.

ACG, American College of Gastroenterology; CBC, complete blood cell count; SIBO, small intestine bacterial overgrowth.

Typical Features of IBS

- Loose/frequent stools
- Constipation
- Bloating
- Abdominal cramping, discomfort, or pain
- Symptoms:
 - Brought on by food intake/specific food sensitivities
 - Dynamic over time (change in pain location, change in stool pattern)

Red Flags for Organic Conditions

- Fever
- Unexplained weight loss
- Rectal bleeding or melena
- Nocturnal diarrhea
- Unexplained iron-deficiency anemia
- Symptom onset after age 50 years of age
- Severe or progressively worsening symptoms
- Family history of organic GI diseases (eg, colon cancer, celiac disease, or IBD)

The Rome Foundation Multidimensional Clinical Profile (MDCP)

- Suggests a framework for classifying mild, moderate, and severe cases of IBS
- Captures multiple dimensions of the patient's experience of the illness
- Integrates information to help guide the plan of clinical care

MDCP Categories

CATEGORICAL DIAGNOSIS	• Standard symptom-based Rome diagnostic criteria
CLINICAL MODIFIERS	• Subcategorizes diagnosis in ways that may affect Tx (eg, IBS-D, IBS-C, & post-infectious IBS)
IMPACT ON DAILY ACTIVITIES	• Quantifies illness impact on patient behaviors and daily function, & influences Tx
PSYCHOSOCIAL MODIFIERS	• Identifies psychological & psychosocial modifiers, & comorbidities that influence experience of illness & affect Tx options (eg, anxiety, depression, suicidal ideation, PTSD, or Hx of abuse)
PHYSIOLOGIC MODIFIERS OF FUNCTION & BIOMARKERS	• Physiologic parameters that may enhance understanding of diagnosis or affect Tx (eg, glucose breath test for SIBO or lactose intolerance test)

MDCP Case Scenario Diagnostic Classifications

MDCP CATEGORY	CASE SCENARIO DIAGNOSTIC CLASSIFICATIONS		
	Mild	Moderate	Severe
Categorical diagnosis	• Meets Rome III or IV criteria for IBS • No red-flag signs or symptoms	• Meets Rome III criteria for IBS • No evidence of celiac disease, microscopic colitis, IBD, or parasitic infestation	• Meets Rome III criteria for IBS • No evidence of celiac disease, microscopic colitis, or IBD
Clinical modifiers	• IBS-D (loose stools during episodes)	• IBS-D (loose-to-watery stools >25% of the time)	• IBS-D (loose-to-watery stools >25% of the time)

MDCP, multidimensional clinical profile

Adapted from: Lucak et al. *Accepted for publication.*

MDCP Case Scenario Diagnostic Classifications (Cont'd)

MDCP CATEGORY	CASE SCENARIO DIAGNOSTIC CLASSIFICATIONS		
	Mild	Moderate	Severe
Impact on daily activities	• Mild • GI symptoms curtail patient activities	• Moderate • GI symptoms interfere with work activities • Mild sleep disturbance	• Severe • GI symptoms cause missed work several days/month • Fecal incontinence
Psychosocial modifiers	• No history of psychological disorders	• Moderate symptom-specific anxiety	• Symptom-specific anxiety due to symptom severity and unpredictability
Physiologic Modifiers of Function & Biomarkers	• None	• None	• None



Management of IBS-D

Goals of Treatment

**Improve
individual
symptoms**

**Ameliorate
global
symptoms**

**Prevent
complications**

**Reduce impact
on the individual
and society**



Case Study #2: 32-year-old Man

■ Medical history

- Diagnosed with traveler's diarrhea 2 years ago by PCP
- Since that time, persistent GI symptoms, including bloating, cramping, and loose, watery stools (3-5 times per day)
- Bowel function was normal prior to the trip



Case Study #2 (cont'd)

■ Treatment history

- Increased fiber intake exacerbates symptoms
- Antidiarrheal medications, useful for fecal urgency and diarrhea, fail to relieve pain and bloating
- Unresponsive to anticholinergics

■ Additional comments

- Patient is frustrated with the lack of effective symptom management



Case Study Discussion

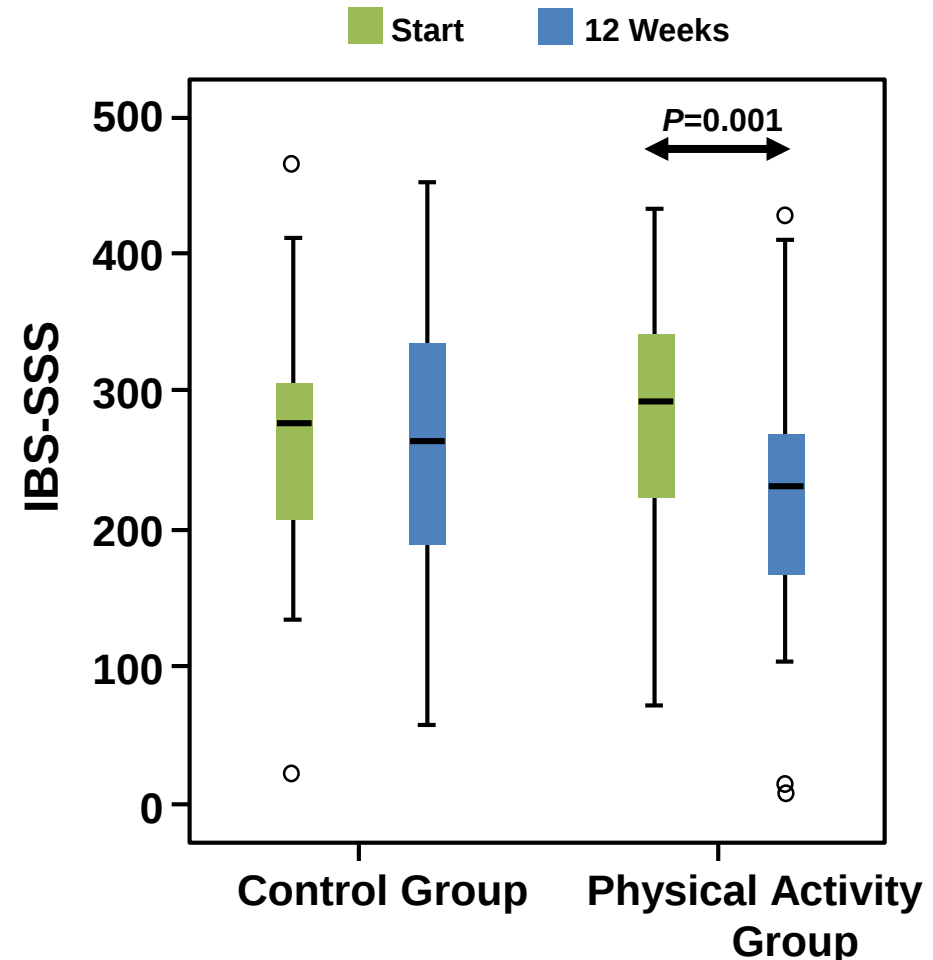
- Lack of symptom control/response to conventional therapies is common
- IBS-D in men vs women
- Precipitation of disease by infection
- Newer pharmacologic management strategies



Nonpharmacological Management of IBS-D

Lifestyle Modifications: Exercise

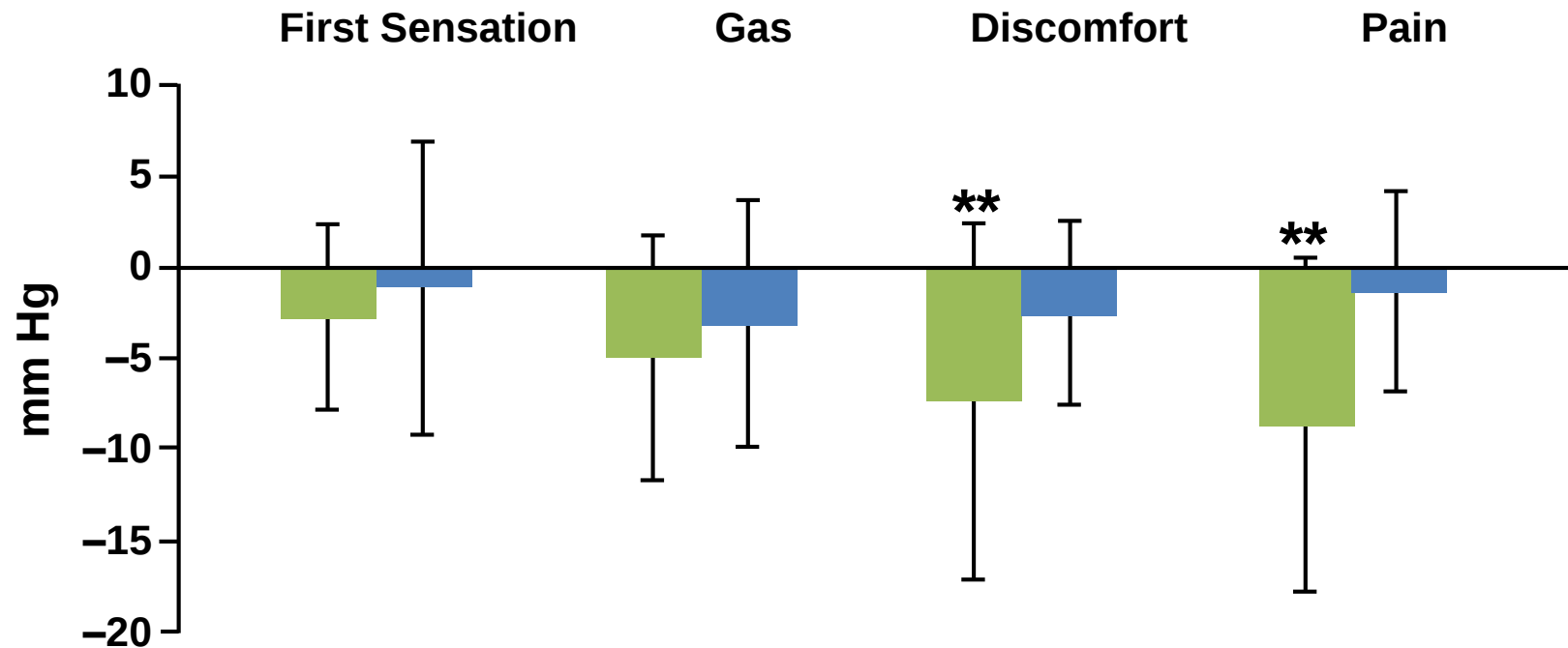
- Prospective, randomized, controlled, open-label study (N=102)
- Increased physical activity was associated with the following:
 - Decreased IBS symptom severity (graph)
 - Improvement on dimensions of IBS-QOL (emotion, sleep, energy, physical functioning, social, and physical role)



Lifestyle Modifications: Sleep Hygiene

- Small exploratory study of women with IBS
- Sleep disturbance (self-reported and objectively measured) predicted exacerbation of next-day IBS symptoms
- Daytime IBS symptoms did not predict subsequent nighttime sleep quality

Implementation of a Low-fat Diet



IBS patients demonstrated increased colonic sensitivity and altered viscerosomatic referral pattern following duodenal lipid infusion.

Soluble vs Insoluble Fiber

Soluble	Insoluble
• Attracts water and turns to gel during digestion • Slows digestion • Sources: – Oat bran, barley, nuts, seeds, beans, lentils, and peas – Some fruits and vegetables – Psyllium (ispaghula)	• Adds bulk to the stool • Decreases GI transit time • Sources: – Wheat bran, vegetables, and whole grains

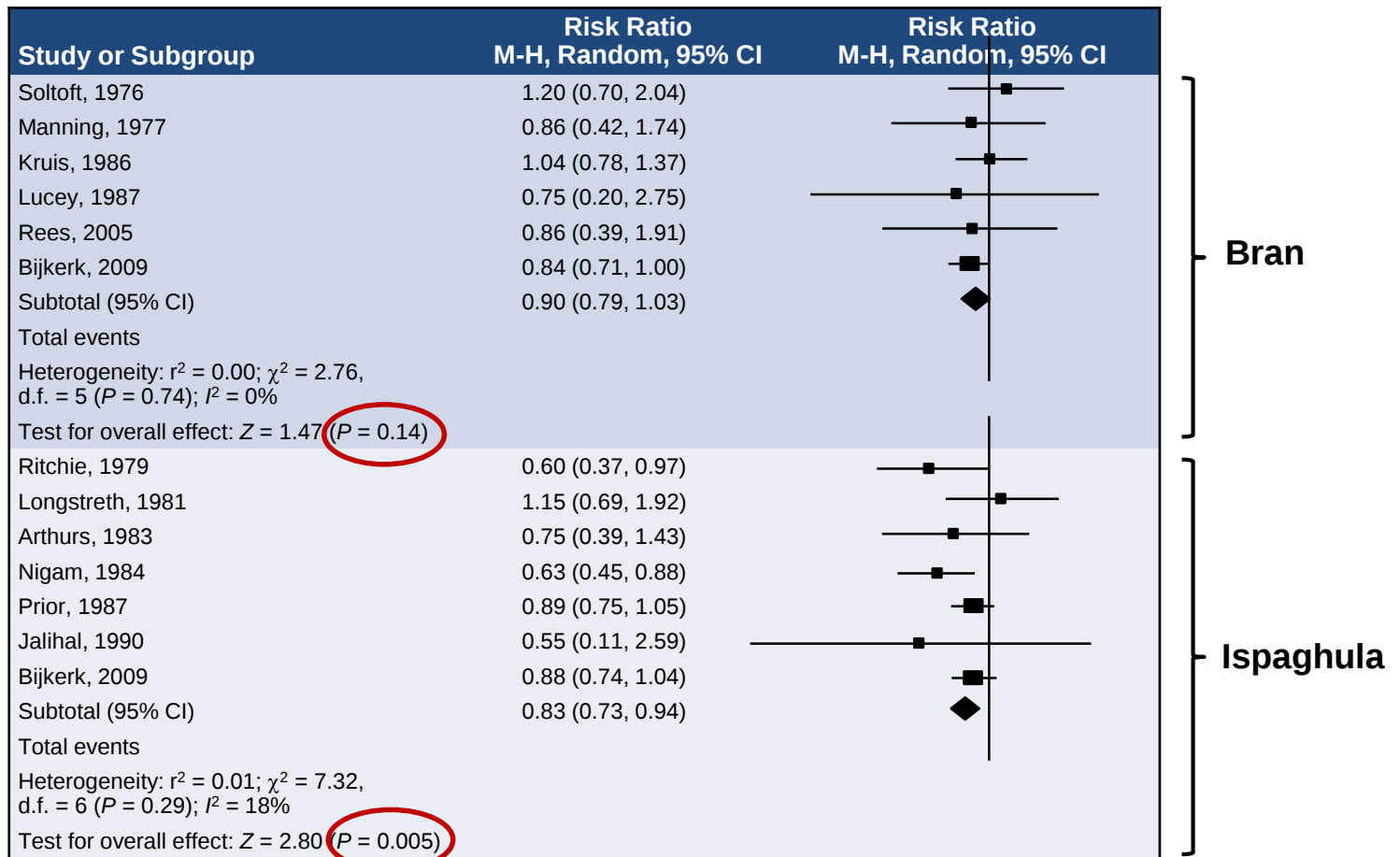
Peppermint Oil

- 5 RCTs (N=392)
- Improvements with ≥ 2 weeks peppermint oil vs placebo:

MEASURE	RR	95%CI
Global symptoms of IBS	2.23	1.78-2.81
Abdominal pain	2.14	1.64-2.79

- AEs were mild and transient in nature with heartburn being the most commonly observed

Soluble Fiber Supplementation Improves Global Symptoms of IBS



Note: Details regarding study weight calculations available in the original publication.
M-H, Mantel-Haenszel

Implementation of a Low-FODMAP Diet for IBS

TEACH PATIENTS

- Assistance from a trained dietician is ideal
- Alternatively, vetted books, web-based resources, and mobile apps may be employed

GAUGE RESPONSE

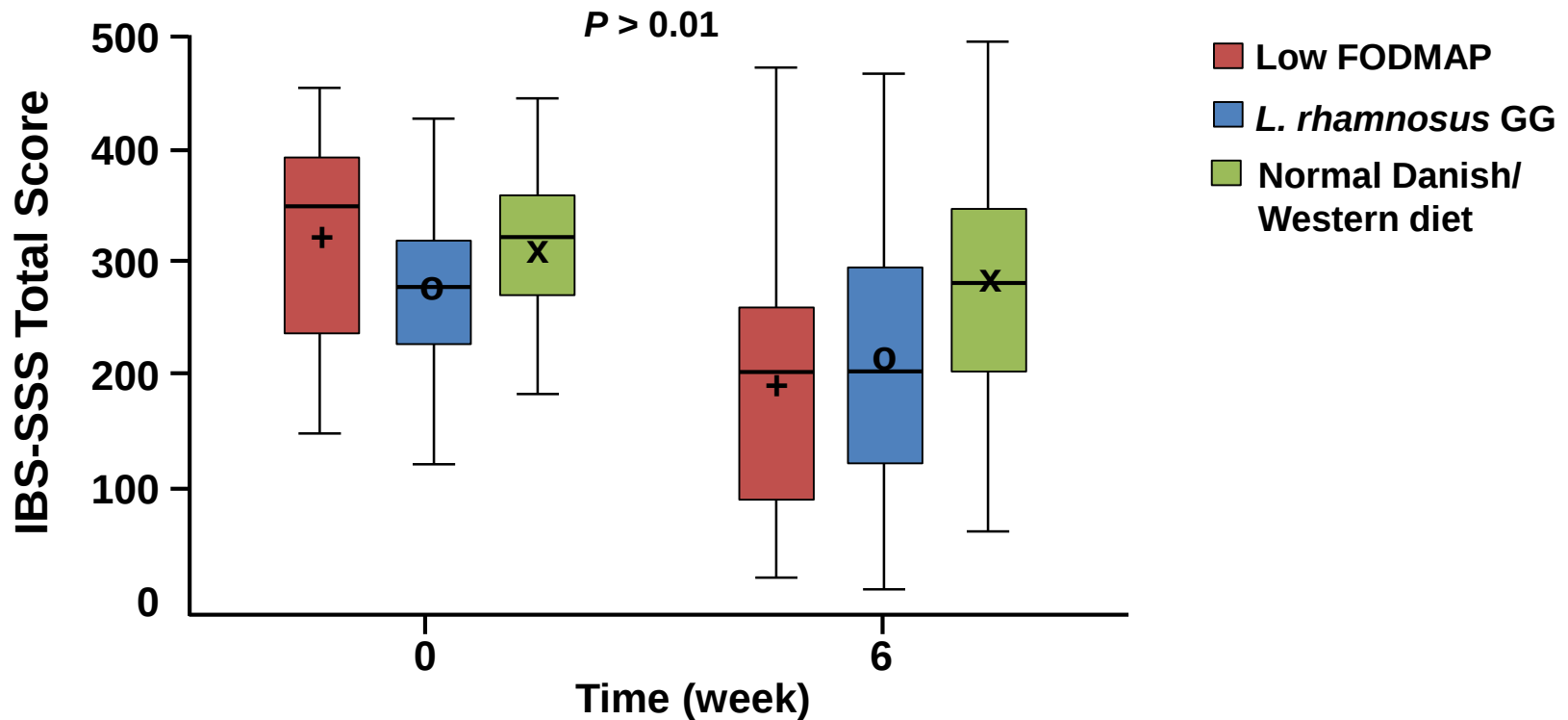
- 2 to 4 week period
- Bloating and abdominal pain are most likely to respond
- Diarrhea is more likely to improve than constipation

REINTRODUCE FOODS

- Foods with individual FODMAPs should be reintroduced in a stepwise manner for responders

- The full low-FODMAP diet is not intended to last a lifetime.
- The low-FODMAP diet is not intended for people without GI symptoms.

Low FODMAP diet vs *Lactobacillus rhamnosus* GG in IBS

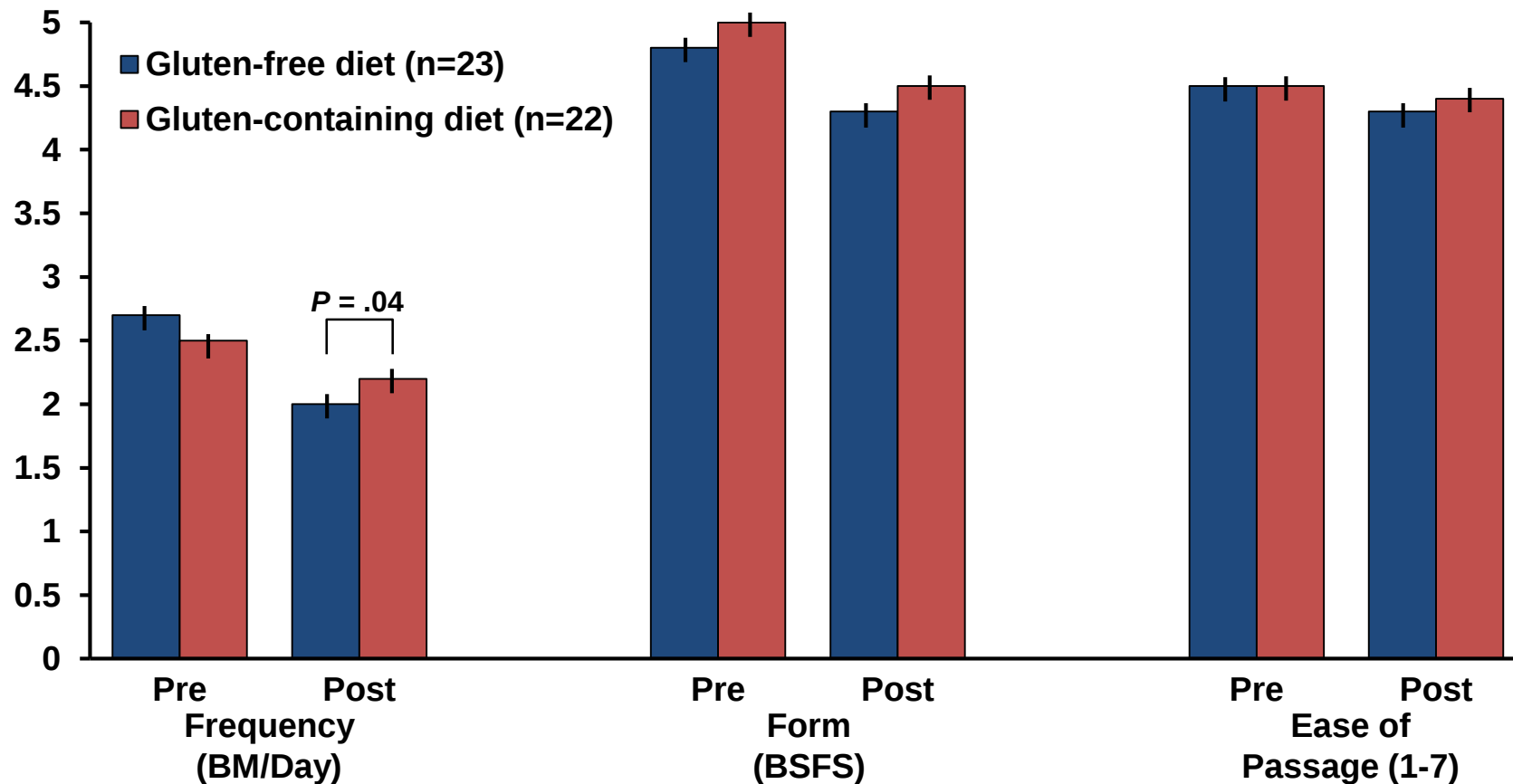


A significant reduction in the IBS-SSS was observed in the low FODMAP and *L. rhamnosus* GG groups compared to the normal Danish/Western diet group at week 6 ($P < 0.01$)

IBS-SSS, Irritable Bowel Syndrome - Severity Scoring System.

Pedersen N, et al. *World J Gastroenterol*;2014;20(43):16215-16226.

Gluten-Free Diet in Patients with IBS-D



BM, bowel movement; BSFS, Bristol Stool Form Scale.

Vazquez-Roque MI, et al. *Gastroenterology*. 2013;144(5):903-911.e903.

Emerging Food-based Approaches: Functional Foods

Functional Foods

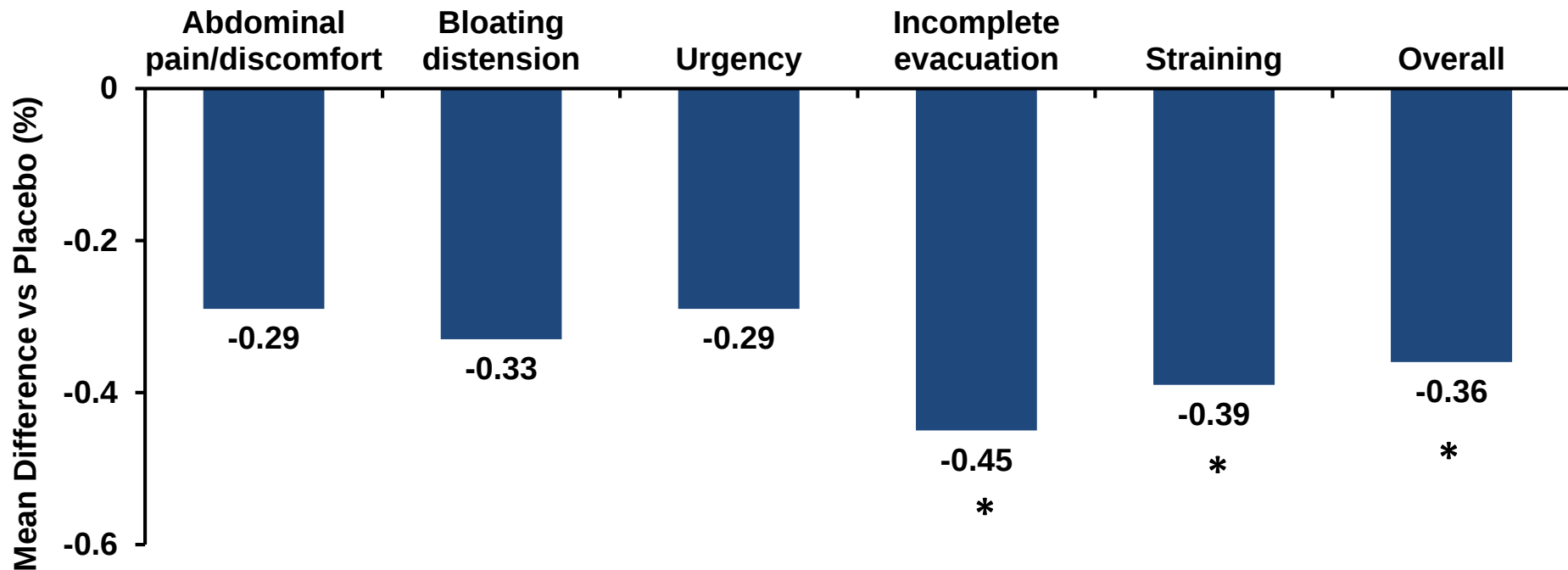
- **Provide health benefits beyond basic nutrition** (eg, disease prevention and/or treatment)
- Include the following:
 - Foods that naturally contain or are enriched/fortified with bioactive components
 - Synthesized food ingredients that provide or are precursors to compounds with health benefits
- Eg, foods containing soluble oat fiber or probiotics

Emerging Food-based Approaches: Medical Foods

Medical Foods

- **For dietary management of a specific disease or condition**
- Given under physician supervision (prescription not required)
- Must comply with FDA-labeling requirements, contain FDA-approved ingredients, and cannot be naturally occurring
- Examples:
 - VSL#3[®] (a medical grade probiotic supplement)
 - Ibgard[®] (sustained-release peppermint oil microspheres)
 - EnteraGam[®] (serum-derived bovine immunoglobulin/protein isolate)

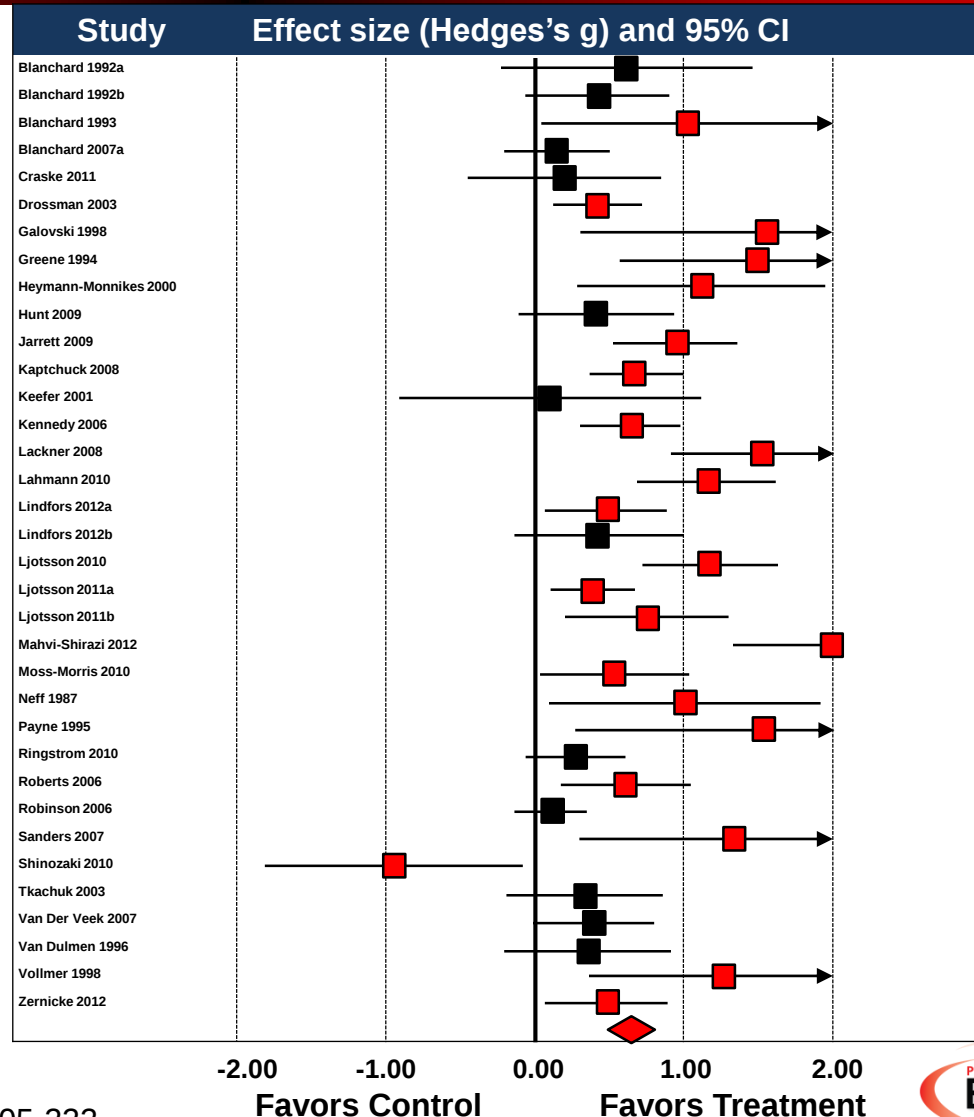
Treatment with *Bifidobacterium infantis* Capsule Reduces Symptoms of IBS



* $P < 0.03$ vs placebo

Impact of Psychological Intervention on IBS Symptoms

- Red shading indicates $P < 0.05$
- Interventions examined in this meta-analysis included a range of therapies:
 - Cognitive
 - Cognitive behavioral
 - Relaxation
 - Psychodynamic
 - Mindfulness
 - Gut-directed hypnosis





Pharmacologic Treatment Options

Conventional Pharmacotherapies for the Treatment of IBS-D

Class (Agents)	Evidence	Efficacy	Common AEs
Antidiarrheals	Very low	• Beneficial for diarrhea, but not global symptoms or pain • Examples include diphenoxylate hydrochloride/atropine sulfate and loperamide)	• Constipation
Antispasmodics	Low	• Some agents offer benefits for global symptoms and pain (eg, hyoscyamine sulfate and dicyclomine hydrochloride)	• Dry eyes/mouth • Sedation • Constipation

AE, adverse effects

Chey WD, et al. *JAMA*. 2015;313(9):949-958.

Newer Agents for the Treatment of IBS-D

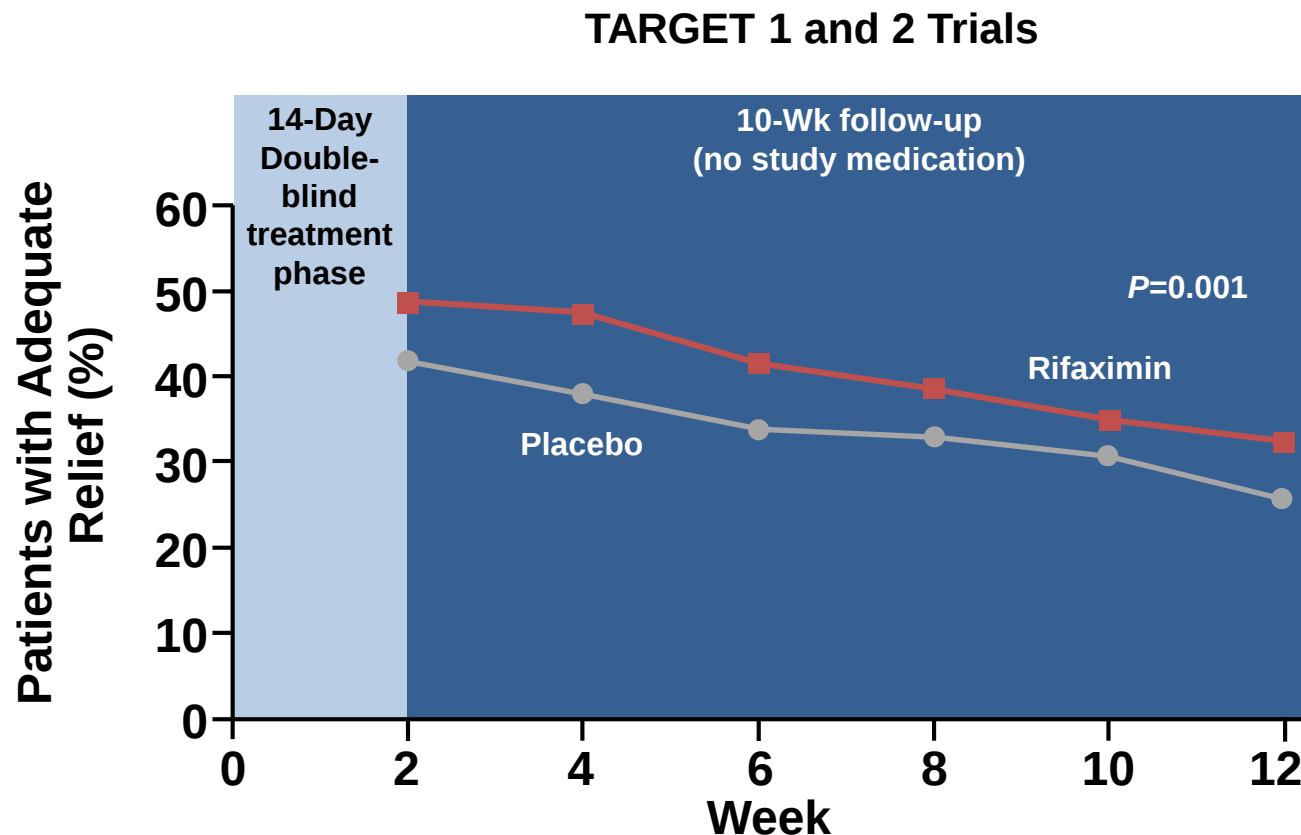
Class (Agent)	Putative Mechanism of Action
Alosetron	Inhibits GI motility via antagonism of 5-HT₃ receptors of the enteric nervous system and possibly within the central nervous system
Eluxadoline	Inhibits gastric emptying, increases sphincter tone, and induces stationary motor patterns via interactions with opioid receptors (agonism at μ- and K-receptors and antagonism at δ-receptors)
Rifaximin	- Is a broad antibiotic against GI aerobic and anaerobic Gram-positive and Gram-negative bacteria (may allow resetting of the microbiota) - Alters the inflammatory environment and bacterial end-products in patients with various GI disorders

Cremonini F et al. *Neurogastroenterology & Motility*. 2003;15(1):79-86.

Pimentel M *Aliment Pharmacol Ther*. 2016;43 Suppl 1:37-49.

Holzer P *Regulatory peptides*. 2009;155(1-3):11-17.

Rifaximin Treatment Is Associated in Sustained Reduction of IBS Symptoms Over 12 Weeks



Two weeks of treatment with rifaximin resulted in a greater percentage of patients achieving adequate relief of global IBS symptoms.

Rifaximin Treatment Improves Symptoms in Patients with Recurrent IBS-D

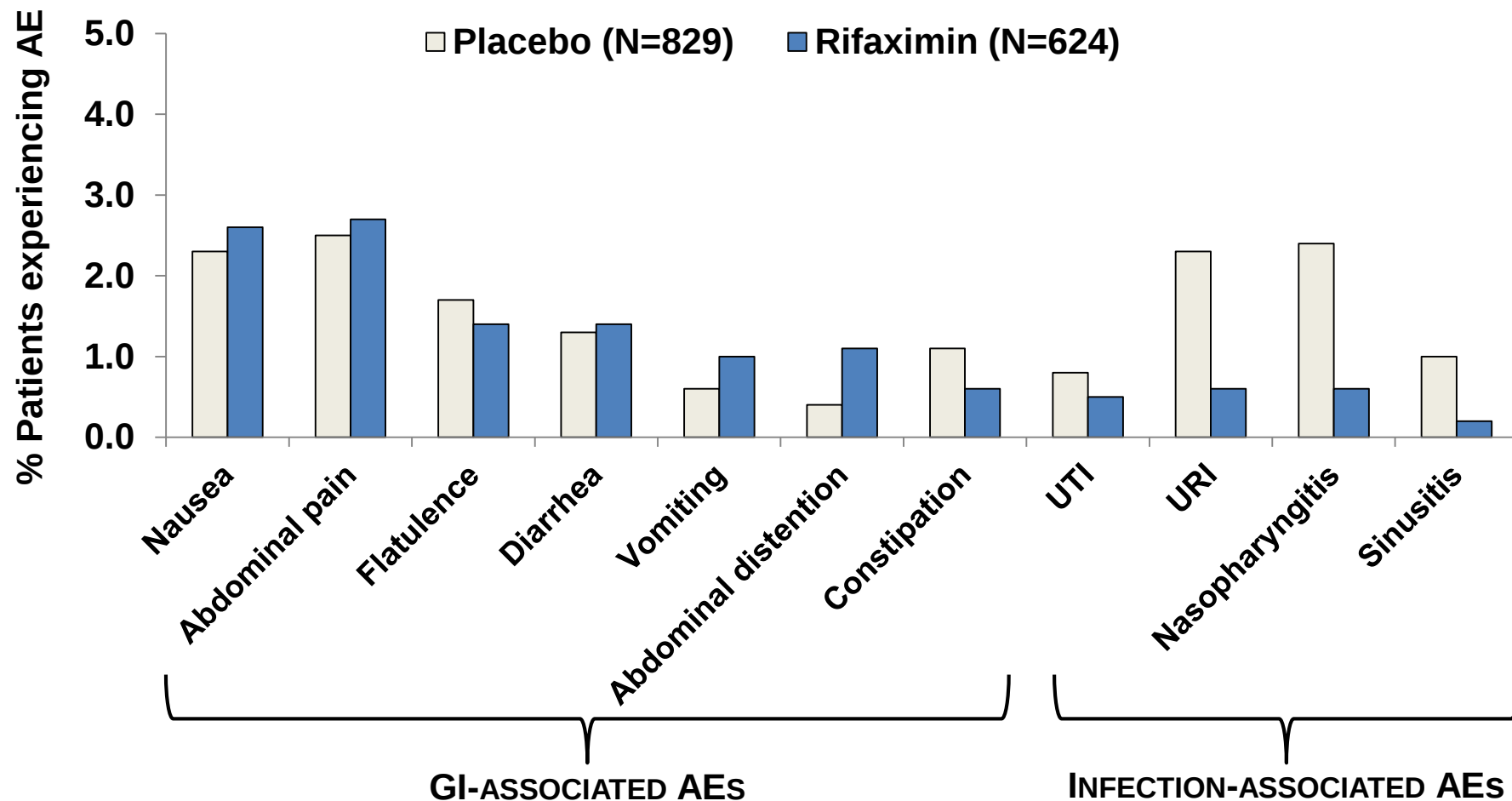
TARGET 3 Trial

	1st Repeat Treatment			2nd Repeat Treatment		
Endpoint	Rifaximin (n=328)	Placebo (n=308)	P Value	Rifaximin (n=328)	Placebo (n=308)	P Value
Urgency	48.5%	39.6%	.0251	46.8%	38.5%	.0355
Bloating	50.3%	42.2%	.0345	47.1%	35.0%	.0017
Abdominal pain	53.0%	43.8%	.0212	52.5%	44.9%	.0549
Stool consistency	45.1%	37.0%	.0241	45.1%	38.5%	.0799

TARGET 3, Targeted, Nonsystemic Antibiotic Rifaximin Gut-Selective Evaluation of Treatment for Non-C IBS

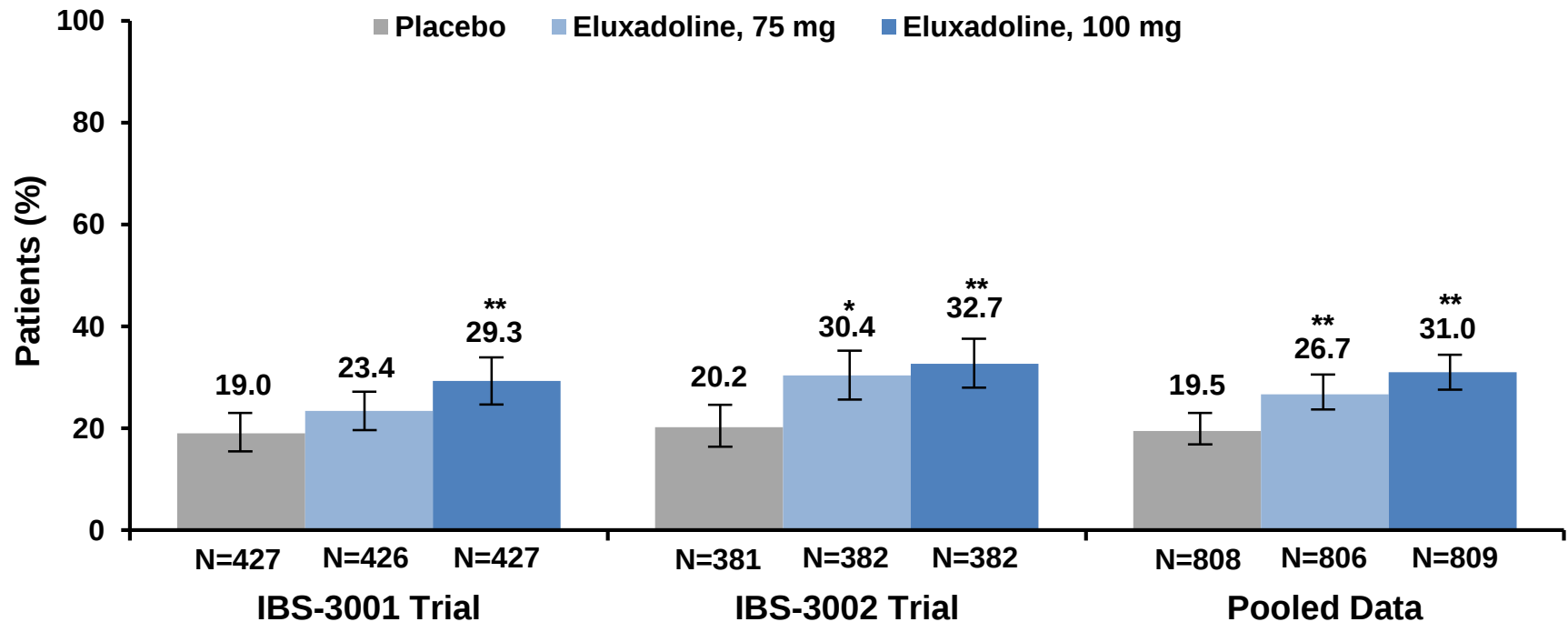
Chey WD, et al. *Gastroenterology*. 2015;148(4):S-69.

Safety and Tolerability of Rifaximin



URI, upper respiratory infection; UTI, urinary tract infection

Eluxadoline Treatment Results in Sustained Reduction of IBS-D Symptoms over 6 Months



Eluxadoline treatment resulted in more patients reporting a $\geq 30\%$ reduction in abdominal pain score and a stool-consistency score < 5 on $\geq 50\%$ of the days[†].

[†]Represents composite primary efficacy end point

* $P < .0$; ** $P < .001$

Lembo AJ, et al. *N Engl J Med*. 2016;374(3):242-253.

Adverse Effects of Treatment with Eluxadoline

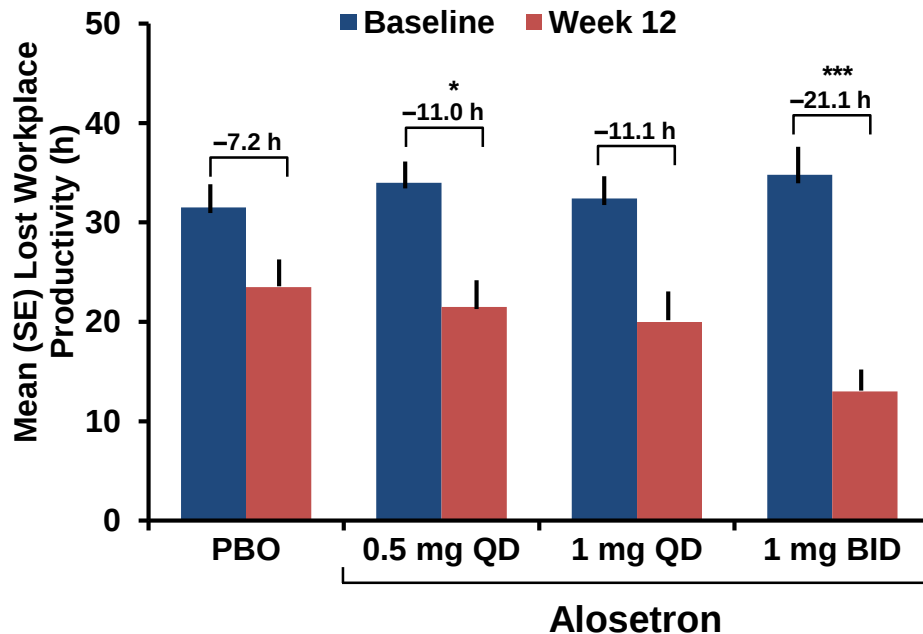
- Most commonly observed AEs:

AE	Placebo (%)	75 mg Eluxadoline (%)	100 mg Eluxadoline (%)
Constipation	2.5	7.4	8.6
Vomiting	1.4	8.1	7.5
Abdominal pain	4.1	5.8	7.2

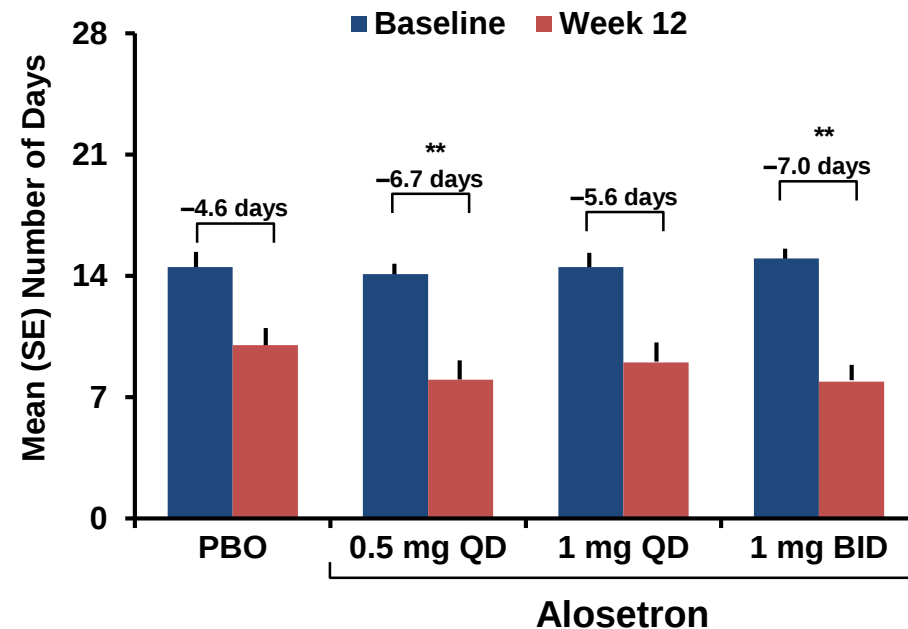
- Pancreatitis developed in 5 (2 in the 75 mg group and 3 in the 100 mg group) of the 1666 patients in the safety population (0.3%)

Impact of Alosetron Treatment in Women with Severe IBS-D

Workplace Productivity



Social/Leisure Activity



Alosetron treatment resulted in improvements in HRQOL, restriction of daily activities, and treatment satisfaction over PBO in women with severe IBS-D.

PBO, placebo; QD, once daily; BID, twice daily.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Cremonini F, et al. *Alimentary Pharmacology & Therapeutics*. 2012;36(5):437-448.

Adverse Effects of Alosetron

	Placebo (N=176)	Alosetron		
		0.5 mg qd (N=175)	1 mg qd (N=172)	1 mg bid (N=176)
Most common AEs (%)				
Constipation	5	9	16	19
Abdominal pain	3	5	6	7
Nausea	6	5	3	6
Sinusitis	6	3	3	6
Headaches	2	5	5	2
AEs for symptoms of potential ischemic colitis* (%)				
Any event	4	9	6	7
Bloody diarrhea or rectal bleeding	2	4	3	3
Worsening of abdominal pain	<1	2	3	3
Bloody diarrhea or rectal bleeding and worsening of abdominal pain	1	2	0	<1

*In 43/44 patients, these events were associated with other medical conditions.

Alosetron: Black Box Warnings

- Infrequent, but serious GI adverse reactions (eg, ischemic colitis, serious complications of constipation) reported; some have resulted in hospitalization and, rarely, blood transfusion, surgery, or death
- Prescribing physicians must be enrolled in Prescribing Program for Lotronex
- Indicated only for women with severe IBS-D that have not responded adequately to conventional therapy
- Discontinue immediately in patients who develop constipation or symptoms of ischemic colitis; do not resume in those who develop ischemic colitis

Antidepressants*

TCAs	• May provide global relief, including reduced abdominal pain
SSRIs	• May improve perception of symptoms • May reduce psychological symptoms that contribute to IBS symptoms
SNRIs	• Beneficial impact on chronic somatic and neuropathic pain • May improve visceral pain, but data are highly limited

- Meta-analysis of 17 RCTs
- IBS symptoms with antidepressant treatment vs placebo
- NNT=4

*Not indicated for the treatment of IBS.

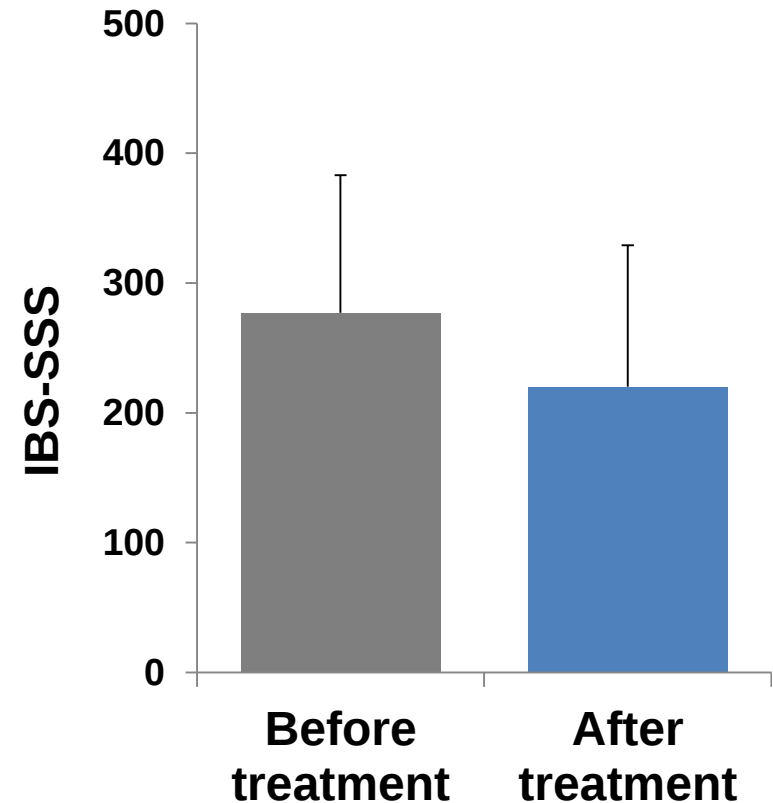
TCAs, tricyclic antidepressants; SSRIs, serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors

Ford AC et al. *Am J Gastroenterol*. 2014;109(9):1350-1365.

Lucak et al. *Accepted for publication*.

Bile Acid Sequestrants

- Increased colonic bile acid exposure influences bowel habit and colonic transit time in patients with IBS
- Open label study of colestipol*:
 - Treatment improved symptoms of IBS (graph)
 - 15/27 patients fulfilled criteria for treatment response (adequate relief $\geq 50\%$ of weeks 5-8)



*Not indicated for the treatment of IBS.



Case Study #3: 45-year-old Woman

■ Clinical presentation and medical history

- 25-year history of recurrent abdominal pain, fecal urgency, and loose stools
- Worsening GI symptoms over the past 1-2 years
 - Increase in number of “bad days”* per week from 1-2 to 4-5
- Abdominal pain and loose stools increase following meals
- Pain improvement following defecation
- Episodes of fecal incontinence
- Recently diagnosed with fibromyalgia

*Defined by severe abdominal pain and fecal urgency with 6-8 loose-to-watery bowel movements/day



Case Study #3: Cont'd

- **Psychosocial effects and social history**
 - High stress at work and at home
 - Travels frequently for work
 - Misses several days of work each month due to GI symptoms
 - Experiences symptom-related anxiety



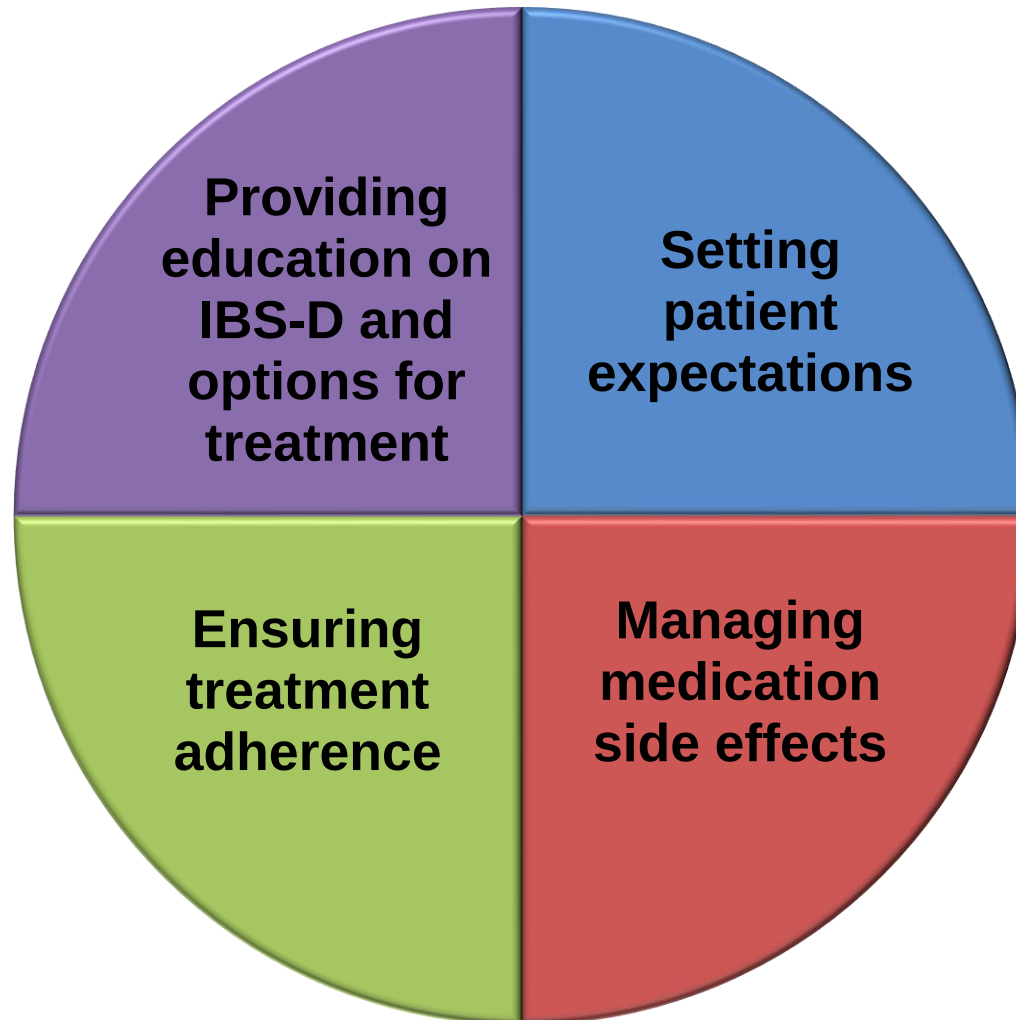
Case Study Discussion

- Consideration of psychosocial disease impact
- Treatment for severe disease
 - Multimodal approach (pharmacologic and nonpharmacologic)
- Role of the patient-provider relationship in managing severe disease
 - Management of therapeutic expectations
 - Promotion of self-monitoring
- Need for specialist referral

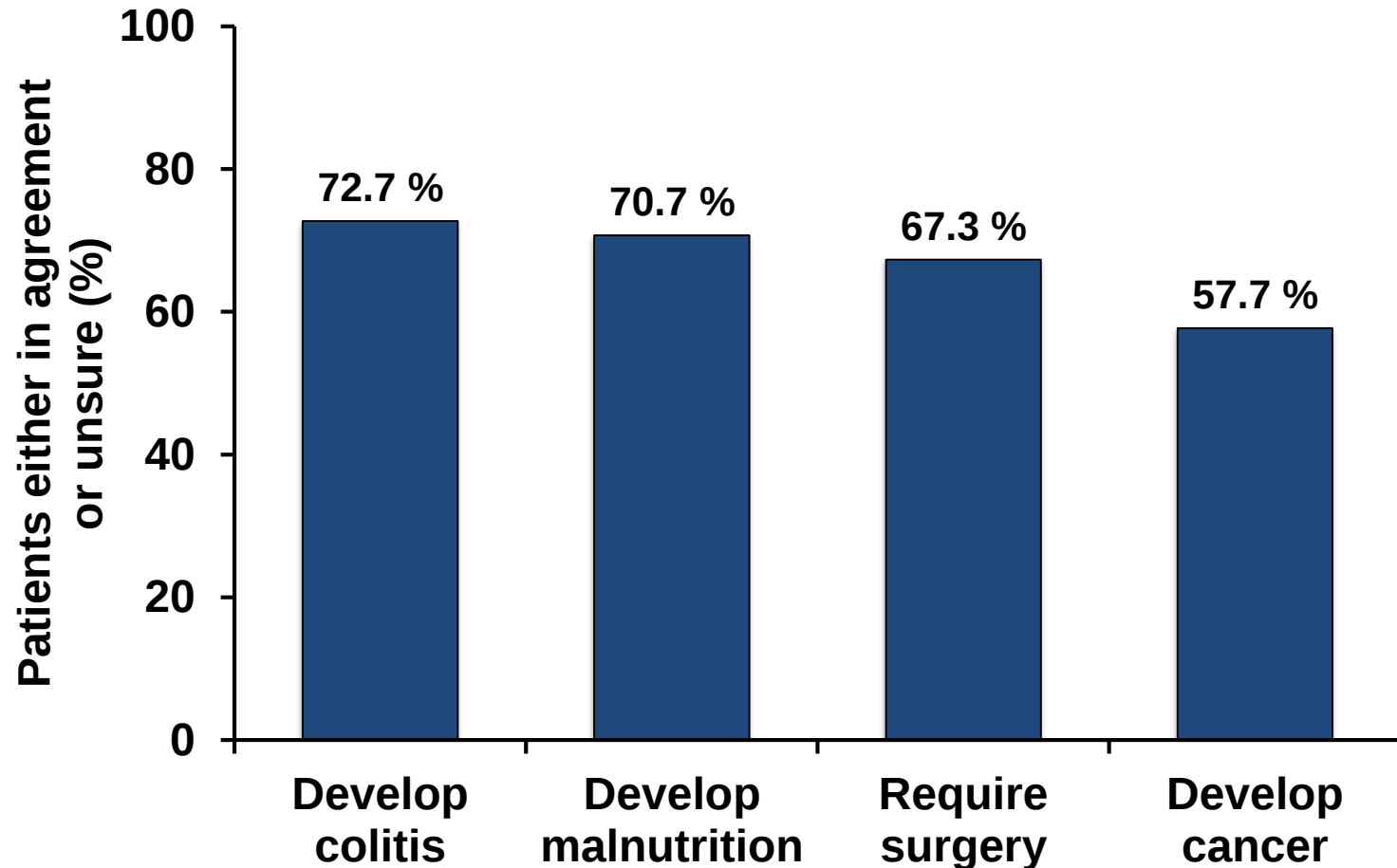


Long-term Management

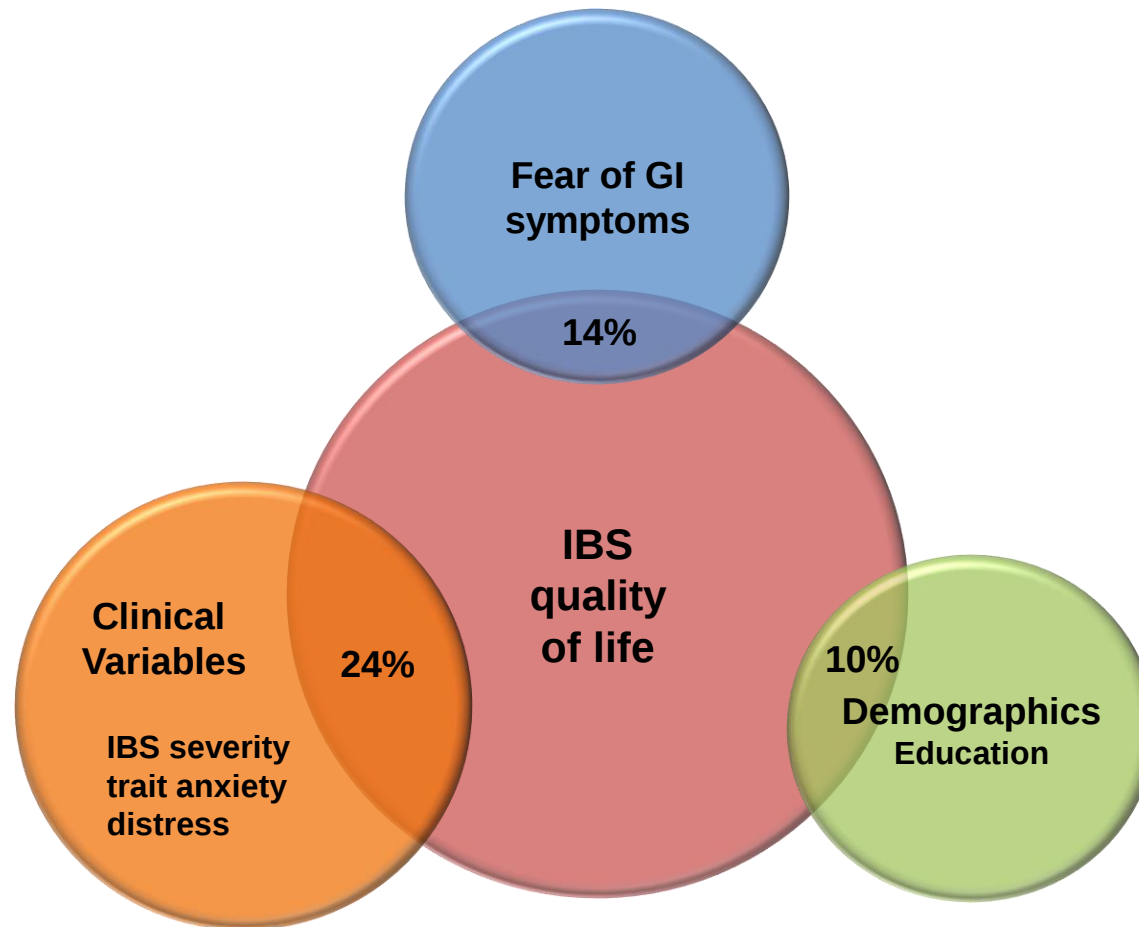
Patient Education and Support



Patient Misconceptions Regarding the Natural History of IBS



Fear of Symptoms Impacts QOL in Patients with IBS: IBSOS Study



Additional IBS Resources

- International Foundation for Functional Gastrointestinal Disorders
 - <http://www.iffgd.org/>
- Institute for Functional Medicine
 - <https://www.functionalmedicine.org/>
- Irritable Bowel Syndrome Association
 - <http://www.ibsgroup.org/ibsassociation.org/>
- IBS Page
 - <http://ibspage.com/>
- IBS CounSEL
 - www.ibscounsel.com/

Summary

- IBS-D is a highly prevalent functional bowel disorder that imposes a tremendous burden due to its pervasive negative impact on the physical, social, and economic well-being of affected individuals
- Diagnosis is based upon a thorough clinical history and physical examination, in conjunction with application of the Rome IV criteria
- Treatment options include several pharmacologic and nonpharmacologic strategies, which have demonstrated efficacy at reducing symptoms of IBS-D and improving patient QOL
- Long-term management should be individualized and include education and support to foster patient understanding of the disease, ensure treatment adherence, and guide therapeutic expectations

Q & A

Thank You!