Irritable Bowel Syndrome

Neil Crittenden

June 5, 2014

I didn’t know that!

- IBS represents what percentage of primary care visits AND gastroenterological referrals?
  - A. 6% and 40%
  - B. 12% and 28%
  - C. 15% and 50%
  - D. 20% and 60%

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  - A. 6% and 40%
  - **B. 12% and 28%**
  - C. 15% and 50%
  - D. 20% and 60%

Overview

- **Pathophysiology**
- Clinical Diagnosis
- Treatment

Pathophysiology

- Old Thoughts:
  - Mechanics of the pain: distension
- New Thoughts:
  - Why is the distension happening?
  - Why the sensitivity?

THE AMERICAN JOURNAL OF GASTROENTEROLOGY

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PII

Correlation of Symptom Criteria With Perception Thresholds During Rectosigmoid Distension in Irritable Bowel Syndrome Patients

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Correlation of Symptom Criteria With Perception Thresholds During Rectosigmoid Distension in Irritable Bowel Syndrome Patients

"The device was programmed to deliver distensions at a rapid volume rate (870 ml/min) to constant pressure plateaus, and to log the sensations (*i.e.,* no sensation, moderate sensation, discomfort, and pain)"

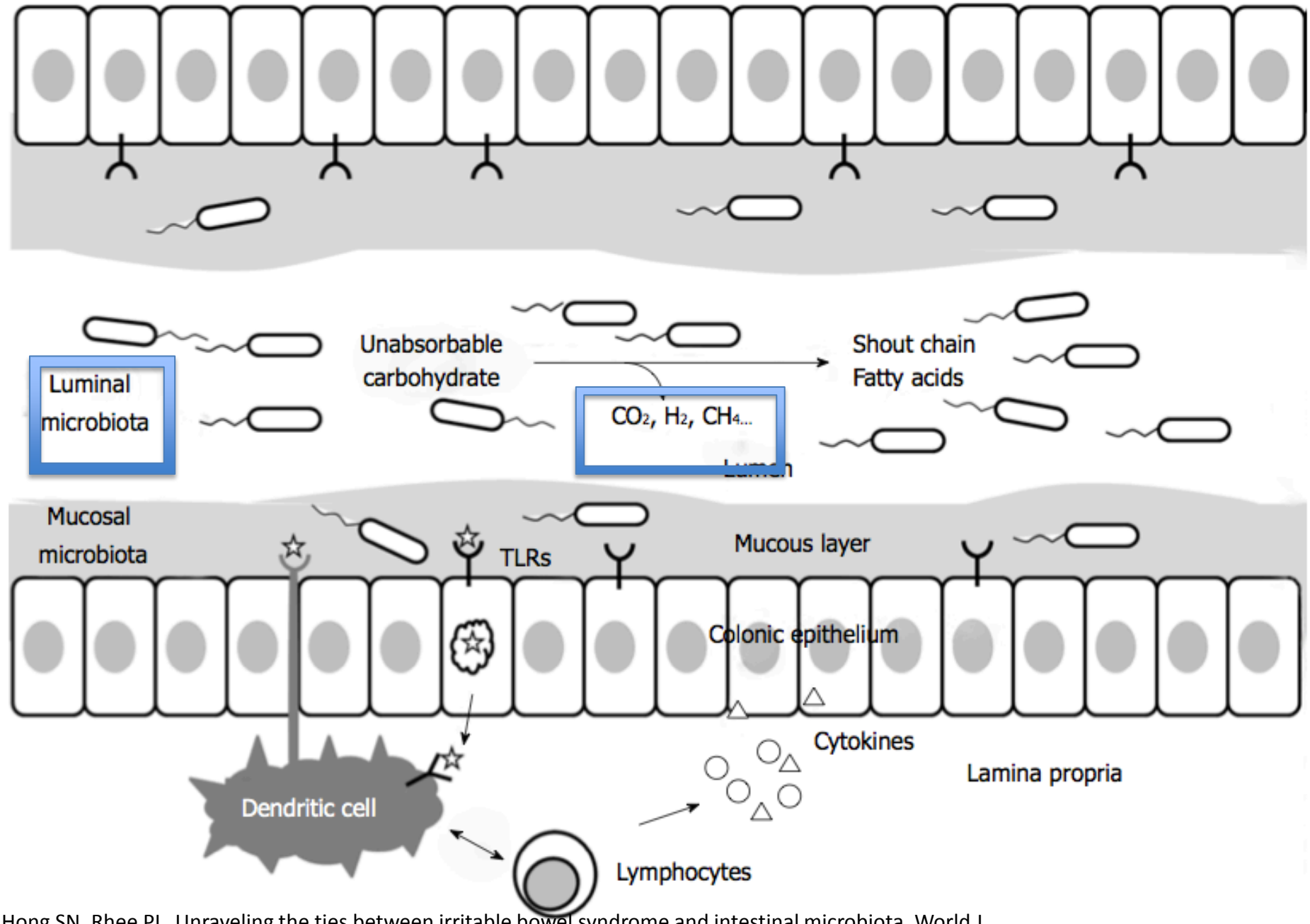
Summary of Results

- Rectal perception thresholds were significantly lower in IBS patients than in healthy controls both before and after sigmoid stimulation

Schmulson M, Chang L, Naliboff B, Lee OY, Mayer EA. Correlation of symptom criteria with perception thresholds during rectosigmoid distension in irritable bowel syndrome patients. Am J Gastroenterol2000 Jan;95(1):152-6.

- ViseralHypersensitivty
  - Colorectal sensitivity is attenuated in IBS after meal intake, and visceral stimulus is higher during stress
- GI Dysmotility
  - Frequent occurrence of High-Amplitude propagated contractions (HAPCs) in IBS-D
  - Pelvic Floor dyssynergia has symptoms attributed to IBS-C
- Brain-Gut Interaction
  - Sensory perception changes by your environment
  - Corticotropin-Releasing Hormone (CRH) is a mediator of stress in this axis. IV CRH exacerbates colonic motility

Lee YJ, Park KS. Irritable bowel syndrome: emerging paradigm in pathophysiology. World J Gastroenterol2014 Mar 14;20(10):2456-69



Hong SN, Rhee PL. Unraveling the ties between irritable bowel syndrome and intestinal microbiota. World J Gastroenterol2014 Mar 14;20(10):2470-81.

Figure 1 Luminal and mucosal intestinal microbiota and roles in gut homeostasis.

Luminal Microbiota

- Majority of the GI microbiota
- Makes gas that makes bloating and flatulence
- Microarray study of 16S rRNA showed:
  - IBS had 2 x greater ratio of *Firmicutes*to *Bacteroides*then controls
  - IBS had 1.5 x increase in *Dorea, Ruminococcus and Clostridium spp.*
  - IBS had 2 x less number of *Bacteroidetes*and 1.5 x less *Bifidobacterium and Facalibacterium*

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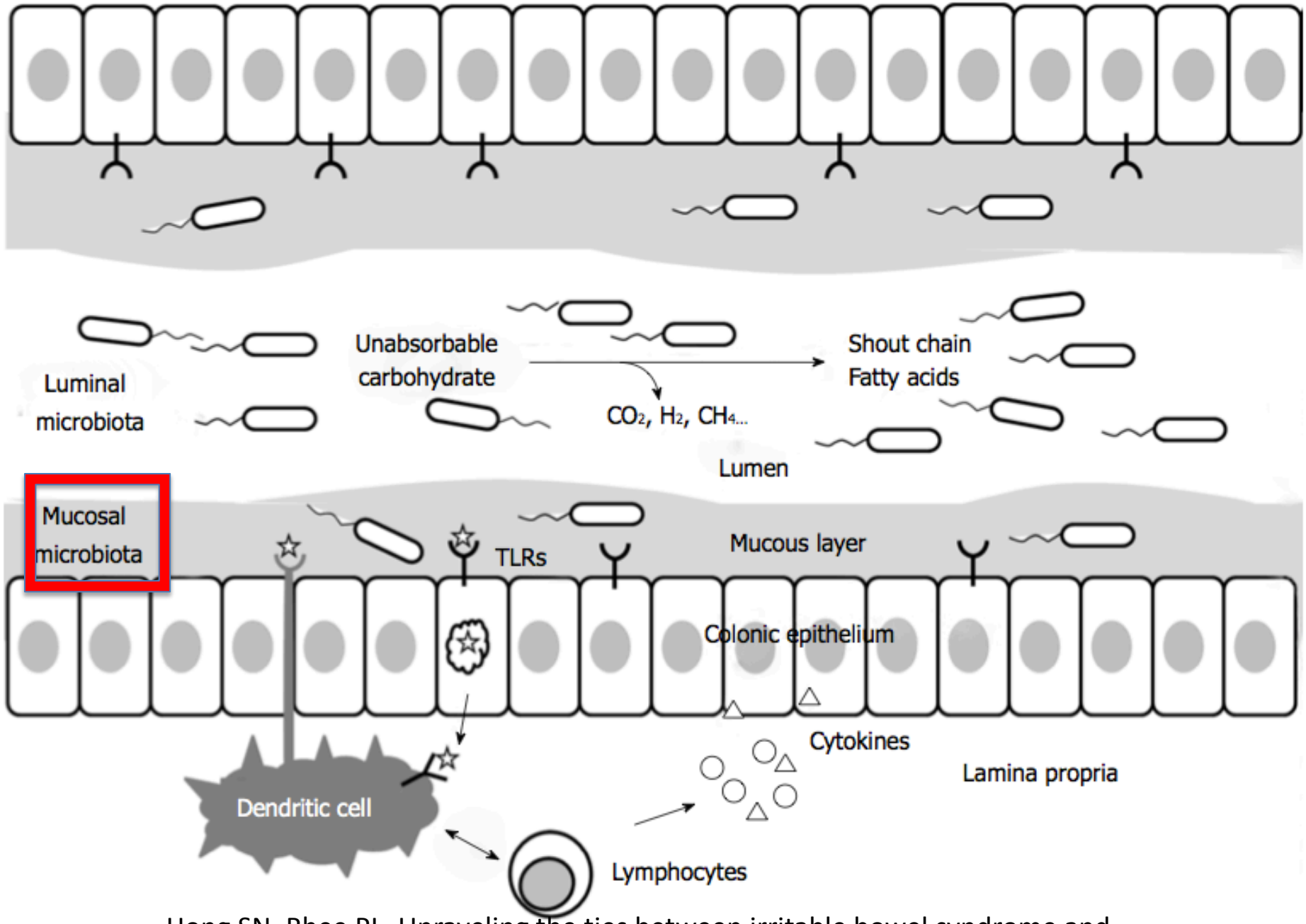

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Figure 1 Luminal and mucosal intestinal microbiota and roles in gut homeostasis.

Mucosal Microbiota

- Influence immune-microbial interactions
- Complex biofilm; only bacteria that can penetrate and possess suitable adhesion proteins can interface with the apical surface
- Luminal interaction involves toll-like receptors (TLR's) and NOD2
  - IBS patient have a differential expression: Increased TLR-4 and TLR-5 and decreased TLR-7 and TLR-8

Hong SN, Rhee PL. Unraveling the ties between irritable bowel syndrome and intestinal microbiota. World J Gastroenterol2014 Mar 14;20(10):2470-81.

Dendritic cells can secrete anti-inflammatory cytokines (IL-10 and TGF-beta)

-*Bifidobacteria*and *Lactobacilli* stimulate IL-10 and TGF-beta

Disturbance of mucosal microbiotoa can up-regulate the immune system and cause inflammation

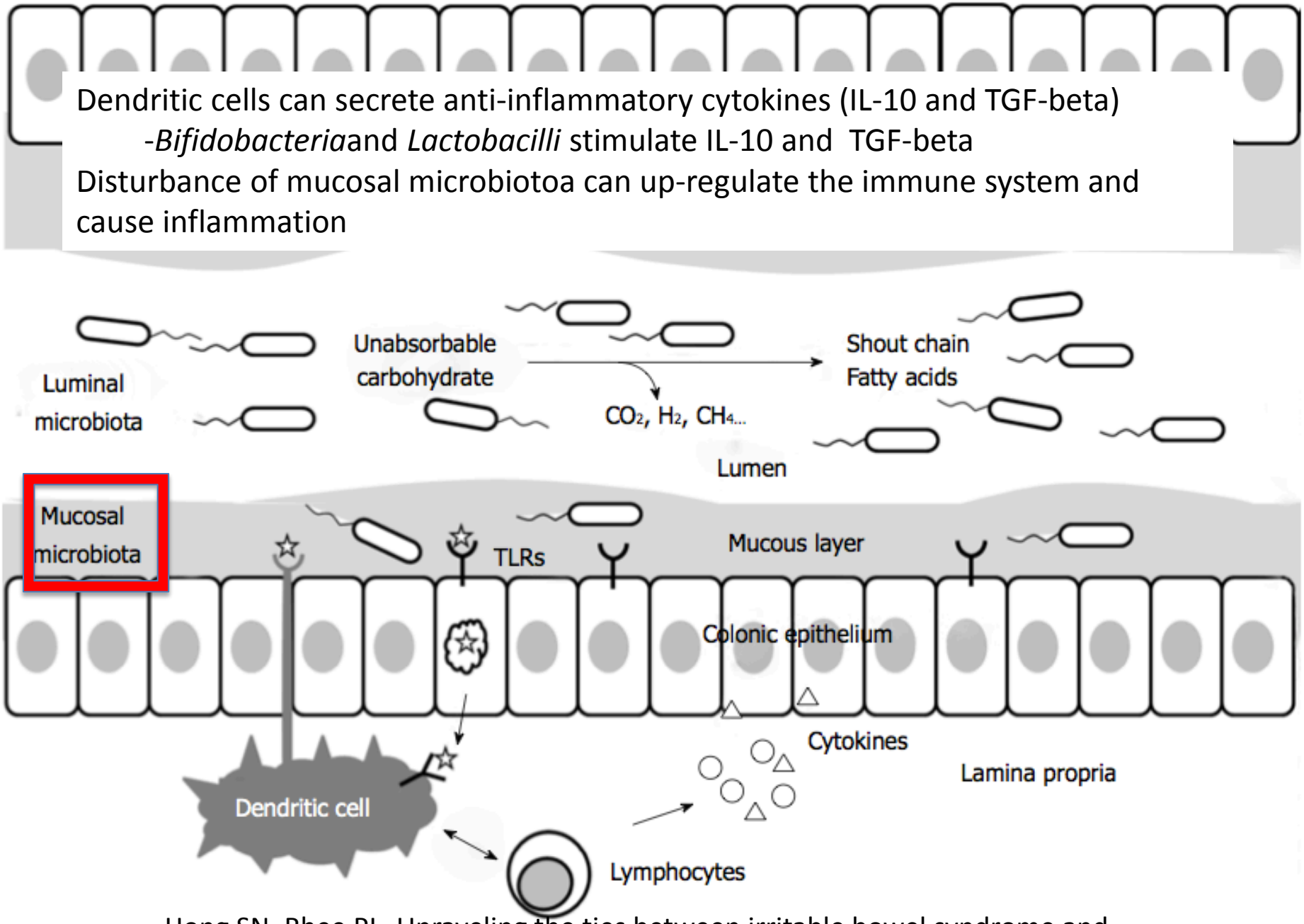

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Figure 1 Luminal and mucosal intestinal microbiota and roles in gut homeostasis.

Overview

- Pathophysiology
- **Clinical Diagnosis**
- Treatment

Introduction

- 1 of 5 adults
- 2.4-3.5 M physician visits per year
- Usually begins before age 35
- Original Rome Criteria formed 1989

Criteria Through The Ages

Table 1
Symptom-based criteria for the diagnosis of IBS

Manning	Rome I	Rome II	Rome III
Abdominal pain relieved by defecation Looser stools with the onset of pain More frequent stools with the onset of pain Abdominal distention Passage of mucus in stools Sensation of incomplete evacuation	>12 wk of continuous or recurrent symptoms of abdominal pain or discomfort: 1. Relieved with defecation or 2. Associated with change in frequency of stool or 3. Associated with a change in consistency of stool Two or more of the following, at least on one-fourth of occasions or days: 1. Altered stool frequency 2. Altered stool form 3. Passage of mucus 4. Bloating or feeling of abdominal distention	>12 wk, which need not be consecutive, in the preceding 12 mo, of abdominal discomfort or pain that has 2 or more of 3 features: Relieved with defecation Onset associated with change in stool frequency Onset associated with a change in form (appearance) of stool	Recurrent abdominal pain or discomfort at least 3 d/mo for past 3 mo, with symptom onset >6 mo before diagnosis, associated with 2 or more of the following: Improvement with defecation Onset associated with a change in frequency of stool Onset associated with a change in stool form (appearance)

GASTROENTEROLOGY 2006;130:1480–1491

Functional Bowel Disorders

GEORGE F. LONGSTRETH,* W. GRANT THOMPSON,† WILLIAM D. CHEY,§ LESLEY A. HOUGHTON,‖ FERMIN MEARIN,¶ and ROBIN C. SPILLER#

*Kaiser Permanente Medical Care Program, San Diego, California; †University of Ottawa, Ottawa, Canada; §University of Michigan, Ann Arbor, Michigan; ‖South Manchester University Hospital, Manchester, United Kingdom; ¶Institute of Functional and Motor Digestive Disorders, Centro Médico Teknon, Barcelona, Spain; and #University Hospital, Nottingham, United Kingdom

Looser stools with the onset of pain
More frequent stools with the onset of pain
Abdominal distention
Passage of mucus in stools
Sensation of incomplete evacuation

discomfort:
1. Relieved with defecation or
2. Associated with change in frequency of stool or
3. Associated with a change in consistency of stool

Two or more of the following, at least on one-fourth of occasions or days:
1. Altered stool frequency
2. Altered stool form
3. Passage of mucus
4. Bloating or feeling of abdom distention

Rome III

Recurrent abdominal pain or discomfort at least 3 d/mo for past 3 mo, with symptom onset >6 mo before diagnosis, associated with 2 or more of the following:

Improvement with defecation

Onset associated with a change in frequency of stool

Onset associated with a change in stool form (appearance)

Criteria Through The Ages

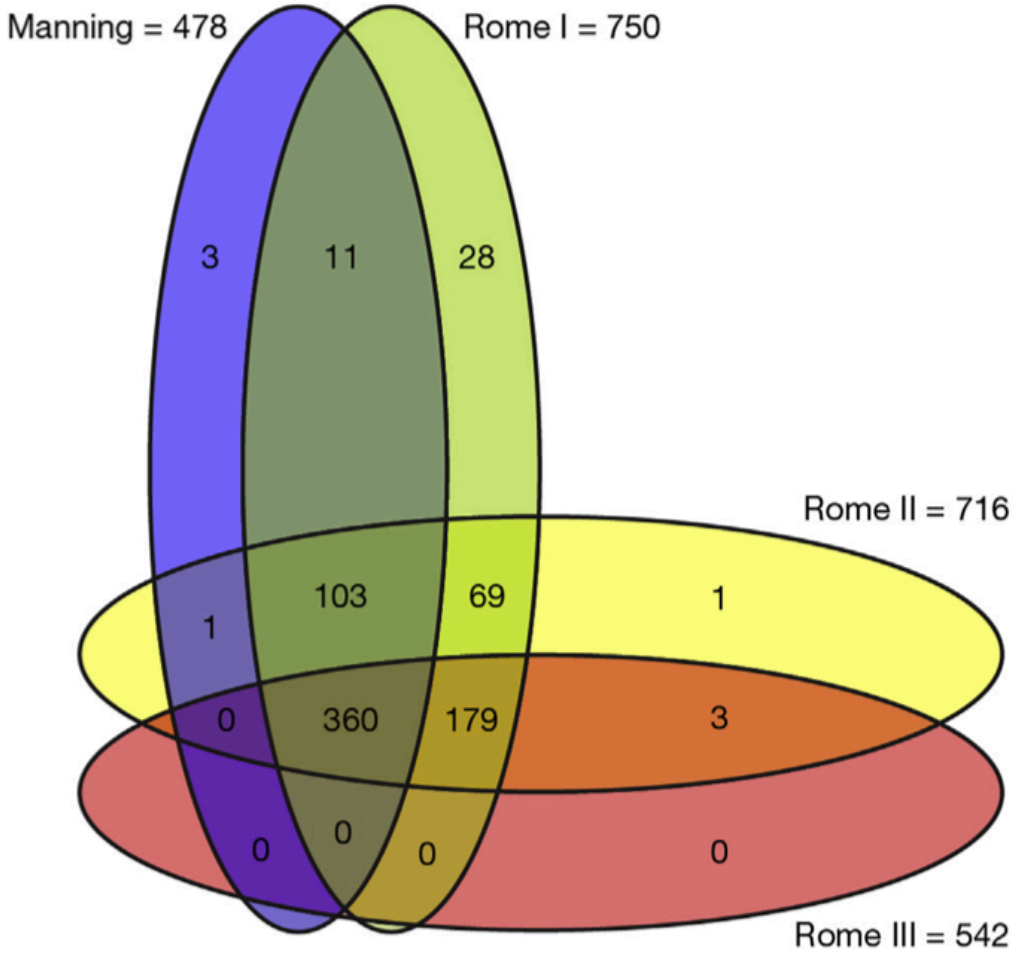

Figure 2. Overlap between diagnostic criteria for irritable bowel syndrome.

Ford AC, Bercik P, Morgan DG, Bolino C, Pintos-Sanchez MI, Moayyedi P. Validation of the Rome III criteria for the diagnosis of irritable bowel syndrome in secondary care. Gastroenterology2013 Dec;145(6):1262-70 e1.

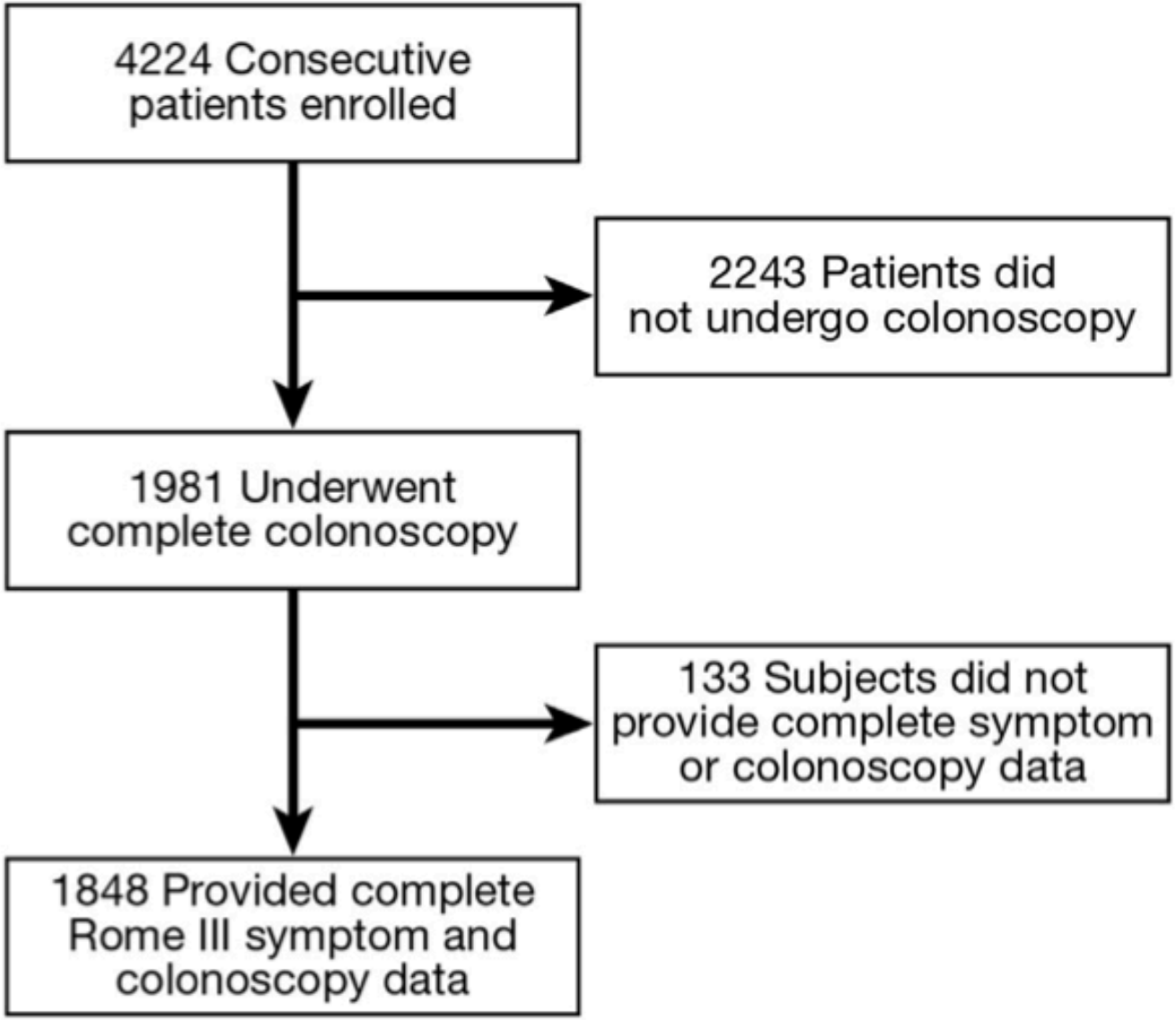

Figure 1. Flow of study participants.

Ford AC, Bercik P, Morgan DG, Bolino C, Pintos-Sanchez MI, Moayyedi P. Validation of the Rome III criteria for the diagnosis of irritable bowel syndrome in secondary care. Gastroenterology2013 Dec;145(6):1262-70 e1.

Validation of Rome III Data

- “555 (30.0%) of the 1848 patients undergoing colonoscopy met the Rome III criteria for IBS.”
- “Among the 365 patients with a diagnosis of IBS according to the reference standard after colonoscopy and distal duodenal biopsy (where appropriate), 251 met the Rome III criteria for IBS, giving a sensitivity of 68.8%”

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2 x 2 Table Time

		“Gold Std” =	**Final Diagnosis**	
	“Test”=Rome III	Really IBS after Endoscopy	OrganicDz	
	Rome III + for IBS			
	Rome III – for IBS			

2 x 2 Table Time

"555 (30.0%) of the 1848 patients undergoing colonoscopy met the Rome III criteria for IBS."

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"Among the 365 patients with a diagnosis of IBS according to the reference standard after colonoscopy and distal duodenal biopsy (where appropriate)…

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n = 555	Rome III + for IBS			
	Rome III – for IBS			
		Total=365		

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…251 met the Rome III criteria for IBS, giving a sensitivity of …. ”

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Sensitivity = True Positive (Rome III= Scope conclusion) = 251 = 68.7%
All IBS Diagnosis (AFTER endoscopy) = 365

2 x 2 Table Time

…251 met the Rome III criteria for IBS, giving a sensitivity of 68.8%"

If you ask the questions, and they don't meet criteria, there's a 31.2% chance the questions are a "False Negative Test Result" and you'll find out they have no organic disease found

		"Gold Std" =	**Final Diagnosis**	
	"Test"=Rome III	Really IBS after endo	OrganicDz	
n = 555	Rome III + for IBS	251		
	Rome III – for IBS			
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Validation of Rome III Data

- “Among 1,483 subjects who were not judged to have IBS according to the reference standard, 1179 did not meetthe Rome III criteria, giving a specificity of 79.5%.”

2 x 2 Table Time

1,483 subjects who were not judged to have IBS according to the reference standard…

		"Gold Std" =	**Final Diagnosis**	
	"Test"=Rome III	Really IBS after endo	OrganicDz	
n = 555	Rome III + for IBS	251		
	Rome III – for IBS			
		Total=365	Total= 1,483	

2 x 2 Table Time

…1179 did not meet the Rome III criteria, giving a specificity of 79.5%."

		"Gold Std" =	**Final Diagnosis**	
	"Test"=Rome III	Really IBS after endo	OrganicDz	
n = 555	Rome III + for IBS	251		
	Rome III – for IBS		1179	
		Total=365	Total= 1,483	

Specificity = True Negative (Rome III= Scope conclusion) = 1,179 = 79.5%
All Organic Diagnosis (AFTER endoscopy) = 1,483

Table 4. Sensitivity, Specificity, Positive and Negative Predictive Values, and Positive and Negative Likelihood Ratios for the Rome and Manning Criteria for Irritable Bowel Syndrome

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive predictive value, % (95% CI)	Negative predictive value, % (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Rome III criteria	68.8 (63.8–73.3)	79.5 (77.4–81.5)	45.2 (41.1–49.4)	91.2 (89.5–92.6)	3.35 (2.97–3.79)	0.39 (0.34–0.46)
Rome I criteria	95.8% (93.2–97.4)	70.6 (68.2–72.8)	45.2 (41.8–48.7)	98.5 (97.6–99.1)	3.26 (3.00–3.53)	0.06 (0.04–0.10)
Manning criteria (≥2 criteria)	85.0 (81.0–88.2)	74.6 (72.3–76.7)	45.8 (42.2–49.5)	95.1 (93.8–96.2)	3.34 (3.04–3.68)	0.20 (0.16–0.26)
Manning criteria (≥3 criteria)	61.9 (56.8–66.7)	81.8 (79.7–83.7)	45.6 (41.3–50.0)	89.7 (88.0–91.2)	3.39 (2.97–3.88)	0.47 (0.41–0.53)
Manning criteria (≥4 criteria)	36.1 (31.3–41.1)	89.5 (87.8–90.9)	45.4 (39.7–51.1)	85.2 (83.4–86.9)	3.42 (2.80–4.18)	0.71 (0.66–0.77)
Rome III criteria with abdominal pain or discomfort replaced by bloating	54.3 (49.2–59.4)	76.4 (74.2–78.5)	36.9 (32.9–41.0)	86.8 (84.9–88.6)	2.31 (2.02–2.63)	0.60 (0.53–0.67)
Rome III criteria with abdominal pain or discomfort and bloating	53.1 (47.9–58.3)	85.1 (83.2–86.9)	46.7 (41.8–51.6)	88.1 (86.4–89.8)	3.58 (3.06–4.17)	0.55 (0.49–0.61)
Rome III criteria with daily abdominal pain or discomfort	29.0 (24.7–33.7)	92.0 (90.5–93.2)	48.1 (41.7–54.5)	83.5 (81.6–85.2)	3.61 (2.87–4.55)	0.77 (0.72–0.82)
Rome III criteria with irregular bowel habit	34.4 (29.8–39.3)	91.1 (89.6–92.5)	49.1 (43.1–55.1)	84.9 (83.0–86.5)	3.88 (3.14–4.81)	0.72 (0.67–0.78)

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Rome II criteria	90.2 (86.8–92.8)	71.7 (69.4–74.0)
Rome I criteria	95.8% (93.2–97.4)	70.6 (68.2–72.8)

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Criteria Through The Ages

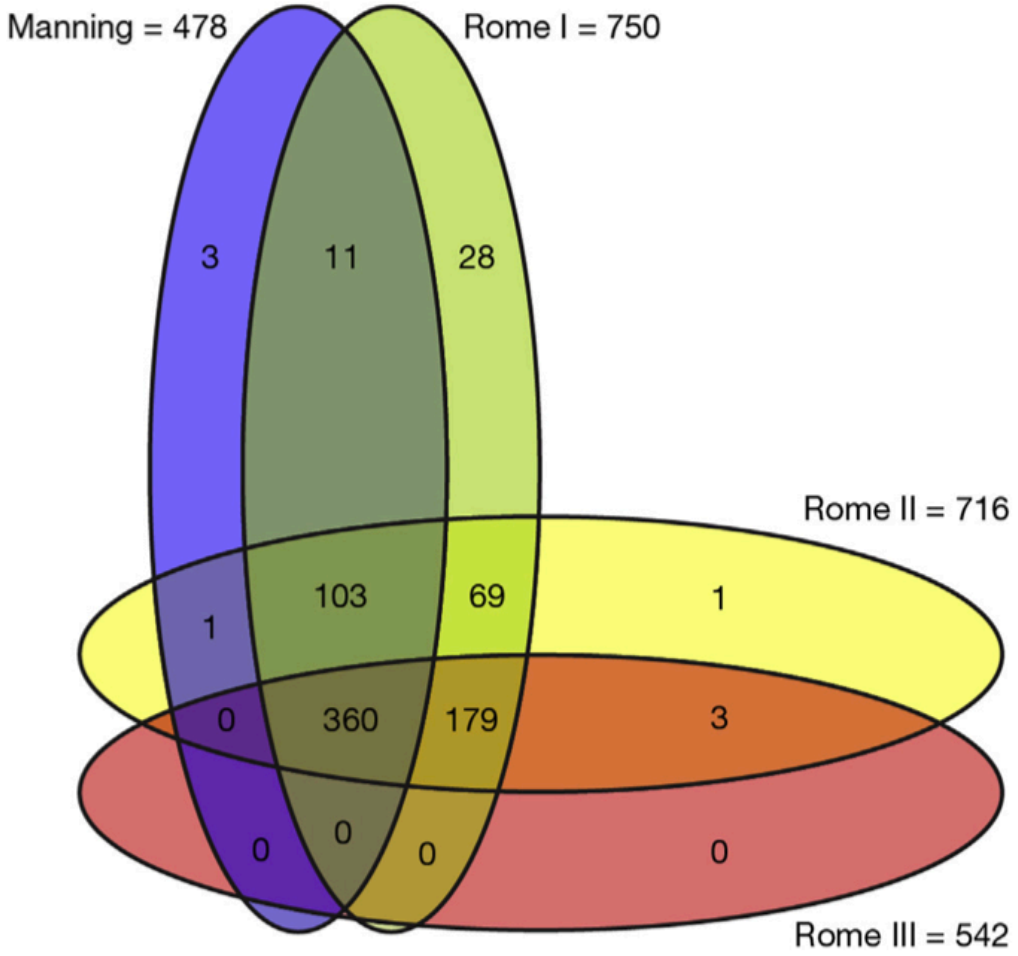

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Table 5. Sensitivity, Specificity, Positive and Negative Predictive Values, and Positive and Negative Likelihood Ratios for the Rome and Manning Criteria for Irritable Bowel Syndrome, Excluding Individuals Reporting Lower GI Alarm Symptoms From the Definition of IBS

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive predictive value, % (95% CI)	Negative predictive value, % (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Rome III criteria	17.4 (13.9–21.5)	95.6 (94.4–96.5)	49.6 (42.0–58.7)	82.1 (80.0–83.6)	3.92 (2.85–5.38)	0.86 (0.83–0.91)
Rome II criteria	23.3 (19.4–27.8)	94.5 (93.2–95.5)	51.7 (44.9–59.5)	82.9 (80.8–84.4)	4.21 (3.20–5.53)	0.81 (0.77–0.86)
Rome I criteria	24.3 (20.3–28.8)	93.9 (92.6–95.0)	50.5 (44.0–58.1)	83.0 (80.9–84.4)	4.01 (3.08–5.22)	0.81 (0.76–0.85)
Manning criteria (≥3 criteria)	13.7 (10.6–17.6)	97.1 (96.1–97.8)	54.1 (45.3–64.6)	81.6 (79.6–83.1)	4.66 (3.18–6.82)	0.89 (0.85–0.93)

Ford AC, Bercik P, Morgan DG, Bolino C, Pintos-Sanchez MI, Moayyedi P. Validation of the Rome III criteria for the diagnosis of irritable bowel syndrome in secondary care. Gastroenterology2013 Dec;145(6):1262-70 e1.

- When patients without alarm symptoms are excluded, Rome III is very specific for IBS

	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Rome III criteria	17.4 (13.9–21.5)	95.6 (94.4–96.5)

- Alarm Symptoms: “Family history of colorectal cancer, rectal bleeding, weight loss or anemia”

Ford AC, Bercik P, Morgan DG, Bolino C, Pintos-Sanchez MI, Moayyedi P. Validation of the Rome III criteria for the diagnosis of irritable bowel syndrome in secondary care. Gastroenterology2013 Dec;145(6):1262-70 e1.

Alarm Features That Suggest Possible Organic Disease

Symptoms
- Weight loss
- Frequent nocturnal awakenings due to gastrointestinal symptoms
- Fever
- Blood mixed in stool

History
- New onset, progressive symptoms
- Onset of symptoms after age 50
- Recent antibiotic use
- Family history of colon cancer or inflammatory bowel disease

Physical Findings
- Abdominal mass
- Stool positive for occult blood
- Enlarged lymph nodes

Wilson JF. In the clinic. Irritable bowel syndrome. Ann Intern Med2007 Jul 3;147(1):ITC7-1-ITC7-16.

Other “Alarm Symptom” Definitions

- Unintended weight loss of more than 4.5 kg (10 lb)
- Fevers or chills
- High-volume (>300 mL/d) diarrhea
- Nocturnal diarrhea
- Family history of gastrointestinal malignancy, IBD, celiac disease
- Older age (>50 years) at onset of IBS symptoms

Furman DL, Cash BD. The role of diagnostic testing in irritable bowel syndrome. GastroenterolClin North Am2011 Mar;40(1):105-19.

2 x 2 Table Time

…1179 did not meet the Rome III criteria, giving a specificity of 79.5%."

		"Gold Std" =	**Final Diagnosis**	
	"Test"=Rome III	Really IBS after endo	OrganicDz	
n = 555	Rome III + for IBS	251	555-251= 304	
	Rome III – for IBS		1179	
		Total=365	Total= 1,483	

Specificity = True Negative (Rome III= Scope conclusion) = 1,179 = 79.5%
All Organic Diagnosis (AFTER endoscopy) = 1,483

Table 3. Prevalence of Organic Disease in Patients Meeting the Rome III Criteria for IBS Compared With Those Who Did Not

	Met Rome III criteria for IBS (n = 555)		Did not meet Rome III criteria for IBS (n = 1293)		
	n	%	n	%	*P* value*
Crohn's disease	48	8.6	84	6.5	.11
Ulcerative colitis	34	6.1	59	4.6	.16
Indeterminate colitis	24	4.3	42	3.2	.27
Colorectal cancer	13	2.3	28	2.2	.86
Lymphocytic colitis	8	1.4	15	1.2	.65
Celiac disease	8	1.4	13	1.0	.47
Radiation enteritis	8	1.4	9	0.7	.18
Collagenous colitis	4	0.7	4	0.3	.25
Nonspecific GI ulceration	3	0.5	2	0.2	.16

**P* value for Fisher's exact test for comparison of categorical data.

Total: 150 of the 555 who met Rome III had Organic Disease

	Met Rome III criteria for IBS (n = 555)	
	n	%
Crohn's disease	48	8.6
Ulcerative colitis	34	6.1
Indeterminate colitis	24	4.3
Colorectal cancer	13	2.3

Rome III Take Home Point

- FITS criteria with NO ALARM symptoms, then you can tell the patient the criteria is “95.6% specific” that they don’t have an organic disease
- ANY alarm symptom, specificity falls to 79.5% and you need to scope
- In the absence of alarm features, the American College of Gastroenterology Task Force does NOT recommend the use of diagnostic testing

Sub-classify

- IBS with constipation: Hard stools >25%, and watery <25%
- IBS with diarrhea: Loose or watery >25% and hard <25%
- Mixed IBS: Hard>25% and watery >25%
- Unsubtyped- insufficient abnormality of stool to classify

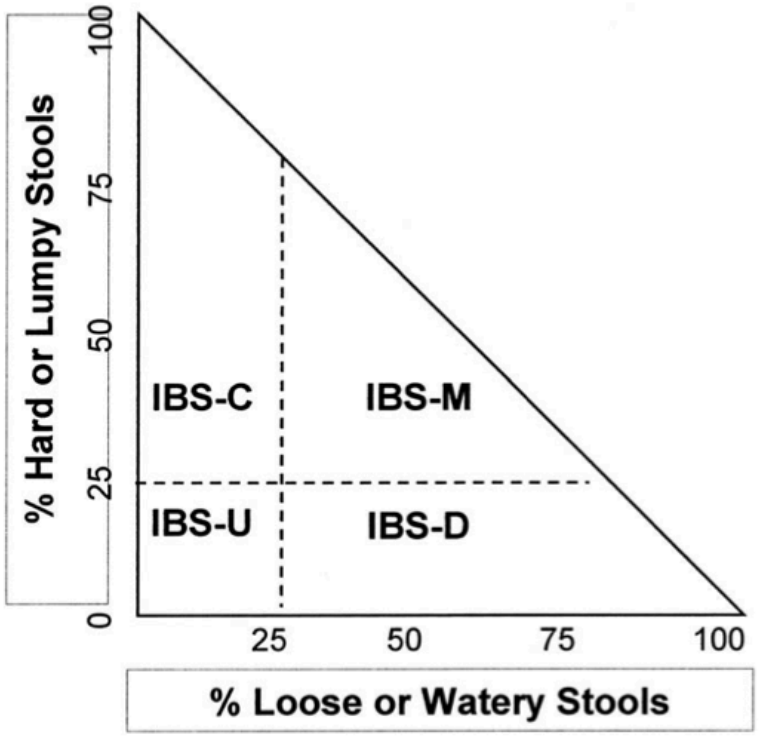


Figure 1. Two-dimensional display of the 4 possible IBS subtypes according to bowel form at a particular point in time. IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, mixed IBS; IBS-U, unsubtyped IBS.

The Upper 4.4%: Diagnostic Testing

- ACG IBS Task Force recommends celiac disease antibodies in nonconstipated IBS symptoms (antiendomysial antibody or anti-tissue transglutaminase)
- It is cost effective to screen IBS patients for celiac disease
- 0.4% of IBS symptom patients are confirmed as celiac disease

Furman DL, Cash BD. The role of diagnostic testing in irritable bowel syndrome. GastroenterolClin North Am2011 Mar;40(1):105-19.

The Upper 4.4%: Diagnostic Testing

- ACG IBS Task Force recommends colonoscopy in patients >50 for colon cancer screening
- If IBS-D, consider random mucosal biopsies to rule out microscopic colitis

Furman DL, Cash BD. The role of diagnostic testing in irritable bowel syndrome. GastroenterolClin North Am2011 Mar;40(1):105-19.

The Upper 4.4%: Diagnostic Testing

- ACG IBS Task Force recommends against stool studies unless there is a relevant travel history or specific alarm features

Furman DL, Cash BD. The role of diagnostic testing in irritable bowel syndrome. GastroenterolClin North Am2011 Mar;40(1):105-19.

The Upper 4.4%: Diagnostic Testing

- In general, there is no algorithm
- Use shared decision making with the patient (risk management of the 4.4%)
- Consider empiric treatment, broadening the differential diagnosis and exploring specific symptom evaluation

Furman DL, Cash BD. The role of diagnostic testing in irritable bowel syndrome. GastroenterolClin North Am2011 Mar;40(1):105-19.

Disease	*Clinical Characteristics*	*Diagnostic Strategy*
Constipation-predominant symptoms		
Strictures due to inflammatory bowel disease, diverticulitis, ischemia, or cancer	Obstipation	Colonoscopy vs. barium enema and flexible sigmoidoscopy
Colonic inertia	Very infrequent bowel movements	Sitzmark transit study
Pelvic floor dysfunction†	Straining, self-digitation	Rectal examination, balloon expulsion study, anoretal manometry, defecography
Neurologic disease†	Concurrent Parkinson disease, autonomic dysfunction (Shy-Drager), multiple sclerosis	History and neurologic examination
Medication†	Opiates, cholestyramine, calcium-channel blockers, anticholinergic medications	Medication history
Hypothyroidism†	Other hypothyroid symptoms and signs	Serum thyroid-stimulating hormone

Diarrhea-predominant symptoms		
Crohn disease	Diarrhea may be from inflammatory exudate, motility changes, small bowel overgrowth, or bile salt malabsorption	Colonoscopy, small bowel barium radiograph
Ulcerative colitis	Likely to have rectal bleeding	Colonoscopy
Microscopic colitis[†]	Generally middle-aged and older women with autoimmune disease (especially thyroiditis)	Colonoscopy/flexible sigmoidoscopy and biopsy
Parasites	*Giardia lamblia* (stream and well water); *Ascaris lumbricoides*, *Entamoeba histolytica* (travel to developing world); *Strongyloides stercoralis* (travel to developing world, Kentucky, or Tennessee)	O + P x 3, stool *Giardia* antigen, metronidazole trial
Clostridium difficile	Recent antibiotics taken	Stool ELISA, flexible sigmoidoscopy for pseudomembranes
Other bacteria	IBS after dysentery may persist for months after infection with bacteria	Compatible history, possible initial positive stool culture
Small bowel overgrowth	Due to severe small bowel dysmotility, partial obstruction, blind loop, or jejunal diverticulosis	Abdominal radiograph, small bowel barium radiograph, lactulose breath hydrogen test, antibiotic trial

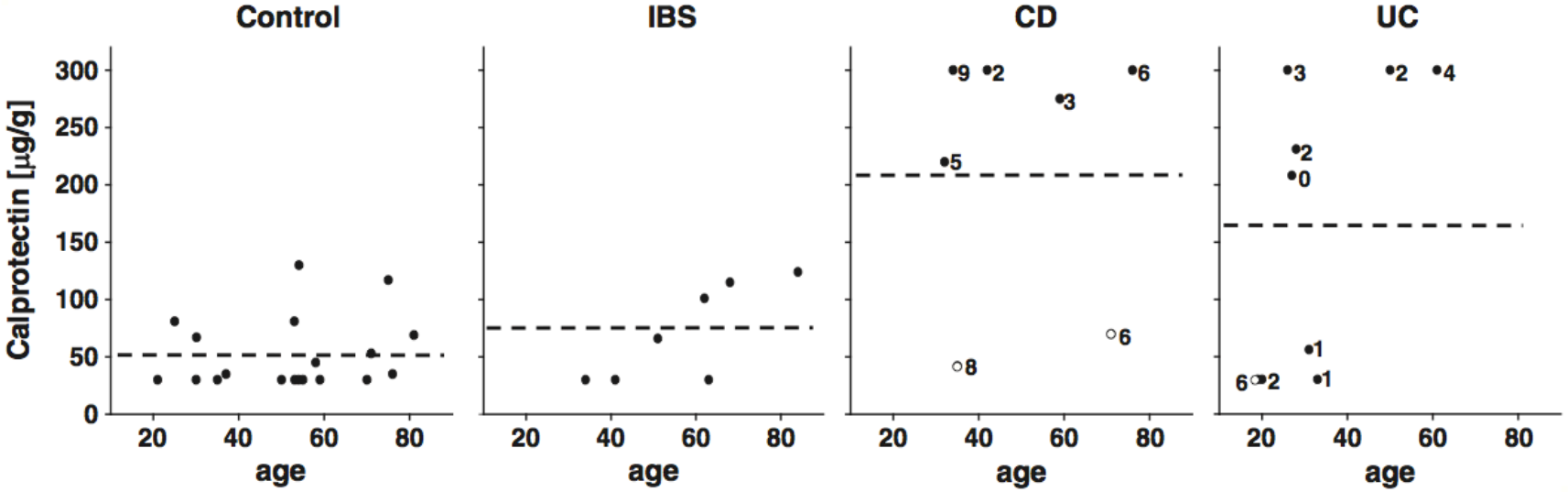
Diarrhea-predominant symptoms		
Sprue† (gluten-sensitive enteropathy)	May present with diarrhea, usually steatorrhea	Usually steatorrhea, positive gliadin, endomysial serum antibodies; endoscopy with small bowel biopsy is gold standard
Lactose intolerance†	Symptoms worse with lactose consumption	Avoidance trial, lactose breath test
Postgastrectomy syndrome	Postprandial symptoms	History of problems worse after gastric surgery
HIV enteropathy	May have chronic GI infections, such as with cryptosporidium, CMV, *Blastocystis hominis*, amoeba	Clinical suspicion, HIV test, low CD4
Gastrointestinal endocrine tumor	Carcinoid, gastrinoma, VIPoma	Urine 5HIAA, fasting gastrin (followed by secretin stimulation test), serum VIP

Pain-predominant symptoms		
Aerophagia, bloating	Patient may be anxious (nervous air swallowing), can be exacerbated by antireflux surgery	Abdominal radiograph with pain
Intermittent small bowel	More likely with history of previous abdominal surgeries	Abdominal radiograph with pain, small bowel barium radiograph

Disease	*Clinical Characteristics*	*Diagnostic Strategy*
Crohn disease	Small intestine or colon involvement	Small bowel barium radiograph colonoscopy
Acute intermittent porphyria	Rare; may have elevated liver enzymes and neurologic symptoms	Serum and urine porphyrins, especially porphobilinogen, and delta aminolevulinic acid
Ischemia	Intestinal angina especially in vasculopaths, food aversion, weight loss, pain 15–40 min after meals	Mesenteric angiogram
Chronic pancreatitis	Alcohol abuse, pain usually more persistent than with usual IBS	Abdominal radiograph for calcifications, CT scan, ERCP, endoscopic ultrasonography
Lymphoma of GI tract	Generally, weight loss	CT scan, small bowel radiograph
Endometriosis	Menstrual-associated symptoms, pelvic symptoms	Laparoscopy

Fecal Calprotectin

- Calprotectin is a protein released by the white blood cells involved in inflammation of the bowel
- High levels suggest pathologic inflammation
- New Rapid Fecal Calprotectin test in Canada, not yet available in the US



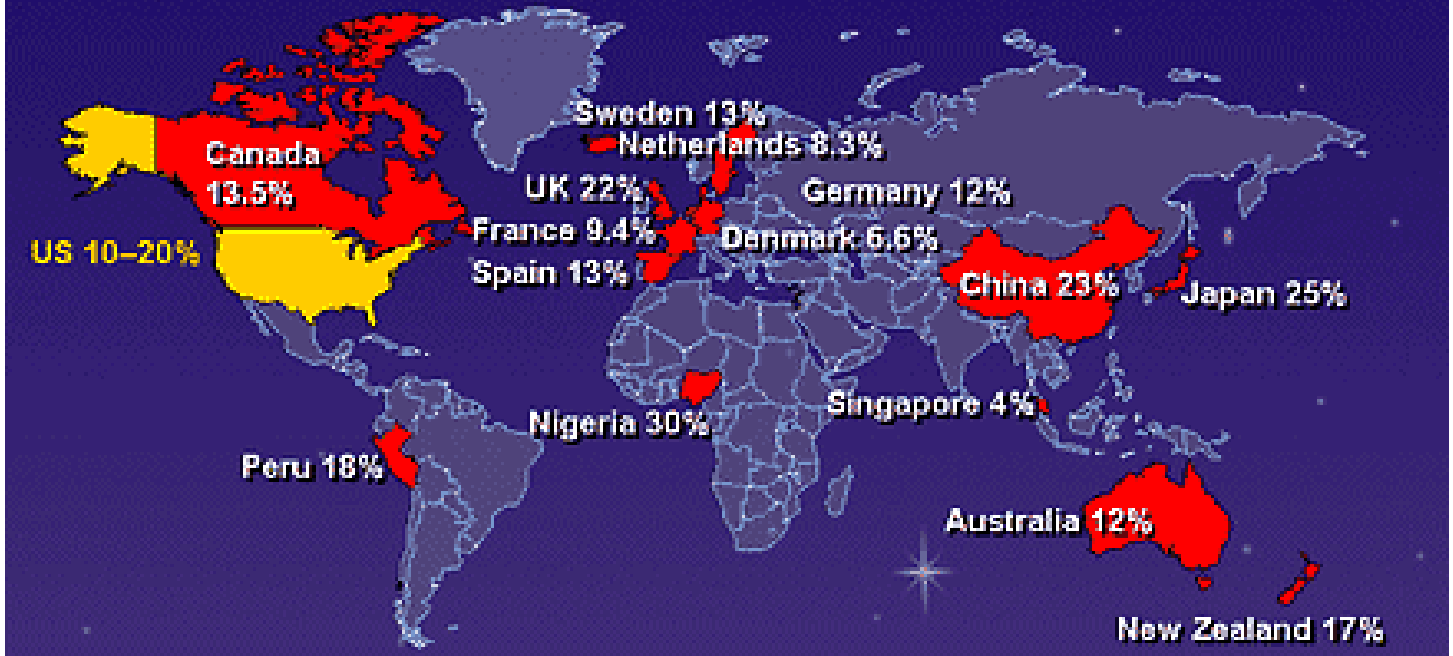
Sydora MJ, Sydora BC, Fedorak RN. Validation of a point-of-care desk top device to quantitate fecal calprotectin and distinguish inflammatory bowel disease from irritable bowel syndrome. J Crohns Colitis2012 Mar;6(2):207-14

Fecal Calprotectin

- 7 different studies have had cut-off leves ranging from 8 to 150 ug/g
- Sensitivity is high for IBD when the cut off is 50 ug/g
- Specificity varied (51-100%), especially at the lower levels

Waugh N, Cummins E, Royle P, Kandala NB, Shyangdan D, Arasaradnam R, Clar C, Johnston R. Faecalcalprotectin testing for differentiating amongst inflammatory and non-inflammatory bowel diseases: systematic review and economic evaluation. Health Technol Assess2013 Nov;17(55):xv-xix, 1-211.

World prevalence of IBS



Adapted from Camilleri et al, Aliment Pharmacol Ther 1997; 11: 3
Muller-Lisner et al, Digestion 2001; 64: 200

Worldwide

- Difficult to assess worldwide prevalence due to a variety of definitions and health care access
- In Cameroon, “many sufferers ascribe their symptoms to the influence of mythological phenomena and will often seek help, in the first instance, from traditional healers, witch doctors, priests, and prayer groups”

Quigley EM, Abdel-Hamid H, Barbara G, Bhatia SJ, Boeckxstaens G, De Giorgio R, Delvaux M, Drossman DA, Foxx-Orenstein AE, Guarner F, Gwee KA, Harris LA, Hungin AP, Hunt RH, Kellow JE, Khalif IL, Kruis W, Lindberg G, Olano C, Moraes-Filho JP, Schiller LR, Schmulson M, Simren M, Tzeuton C. A global perspective on irritable bowel syndrome: a consensus statement of the World Gastroenterology Organisation Summit Task Force on irritable bowel syndrome. J Clin Gastroenterol2012 May-Jun;46(5):356-66.

Socioeconomic Status

- 440,822 Young Israeli Adults serving 2005-2011
- IBS Dx or Worsening of Symptoms:
  - Higher Socioeconomic Status had a Hazard Ratio = 1.629 (95% CI 1.328-1.999)
  - Education >11 years, HR=1.674, (95% CI 1.019-2.751)
  - Noncombat military position, HR = 1.196 (95% CI 1.024-1.397)

Carter D, Beer-Gabel M, Tzur D, Levy G, Derazne E, Novis B, Afek A. Predictive Factors for the Diagnosis of Irritable Bowel Syndrome in a Large Cohort of 440,822 Young Adults. J Clin Gastroenterol2014 Mar 14.

Socioeconomic Status

- IBS Dx or Worsening of Symptoms
  - Israeli Birth (HR 1.362, 95% CI =1.084-1.712)
  - Jewish Ethnicity (HR 2.089 95% CI=1.344-3.248)
- Protective for the diagnosis of IBS (less Sx)
  - Middle Eastern (HR 0.739 95% CI=0.617-0.884)
  - North African / Ethoiopian (HR 0.702 95% CI=0.585-0.842)

Carter D, Beer-Gabel M, Tzur D, Levy G, Derazne E, Novis B, Afek A. Predictive Factors for the Diagnosis of Irritable Bowel Syndrome in a Large Cohort of 440,822 Young Adults. J Clin Gastroenterol2014 Mar 14.

Socioeconomic Status

- Protective for the diagnosis of IBS (less Sx)
  - Rural settlement HR=0.705, 95% CI 0.561-0.886
  - Overweight HR = 0.744, 95% CI 0.589-0.941
  - Obesity HR = 0.698, 95% CI 0.510-0.95

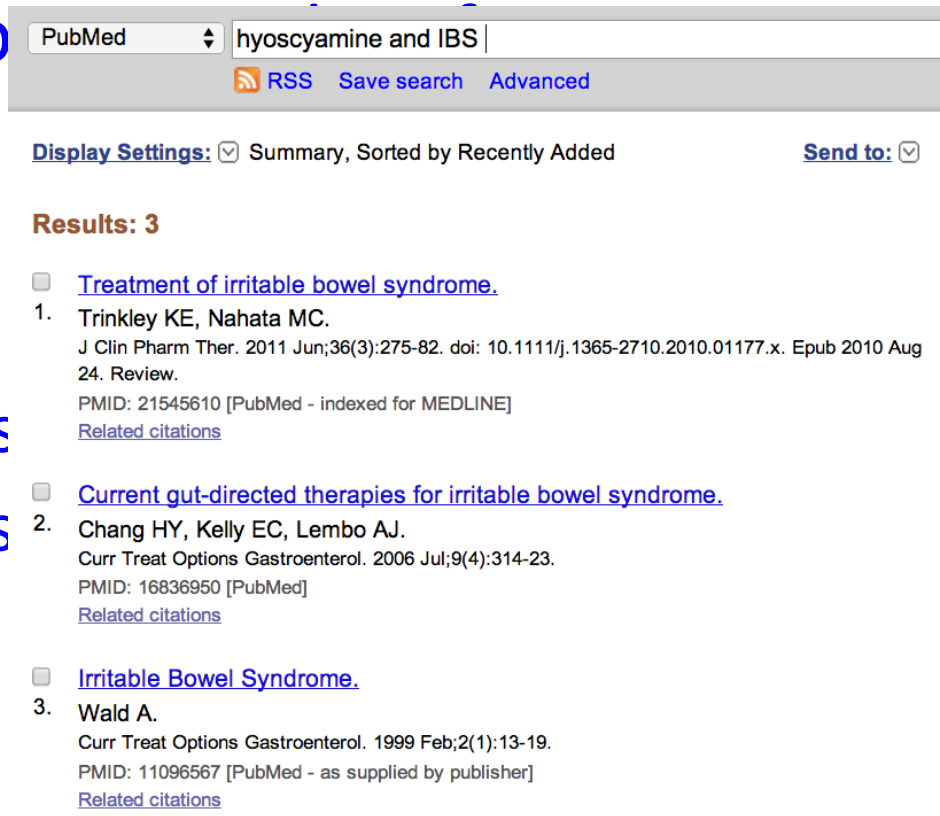
Carter D, Beer-Gabel M, Tzur D, Levy G, Derazne E, Novis B, Afek A. Predictive Factors for the Diagnosis of Irritable Bowel Syndrome in a Large Cohort of 440,822 Young Adults. J Clin Gastroenterol2014 Mar 14.

I didn't know that!

- Levsin (hyoscyamine) is a common treatment for IBS. How many clinical trials has it been tested in for IBS and how many hits for "hyoscyamine and IBS" are on PubMed ?
  - A. 4 trials and 387 hits
  - B. 1 trial and 3,385 hits
  - C. 7 trials and 1,420 hits
  - D. No trials and 58 hits
  - E. No trials and 3 hits

practise for IBS symptoms. Of the antispasmodics available in the US, only peppermint oil has been studied for treating all IBS subtypes; hyoscyamine has not been studied in a controlled fashion. Hyo-

- Levsin (hyoscyamine) is a common treatment for IBS. How many clinical trials has it been tested in for IBS and ho
  "hyoscyamine and IBS"
  - A. 4 trials and 387 hits
  - B. 1 trial and 3,385 hits
  - C. 7 trials and 1,420 hits
  - D. No trials and 587 hits
  - **E. No trials and 3 hits**



Overview

- Pathophysiology
- Clinical Diagnosis
- **Treatment**

Treatments

- There are as many treatment options as there are associated symptoms of IBS…

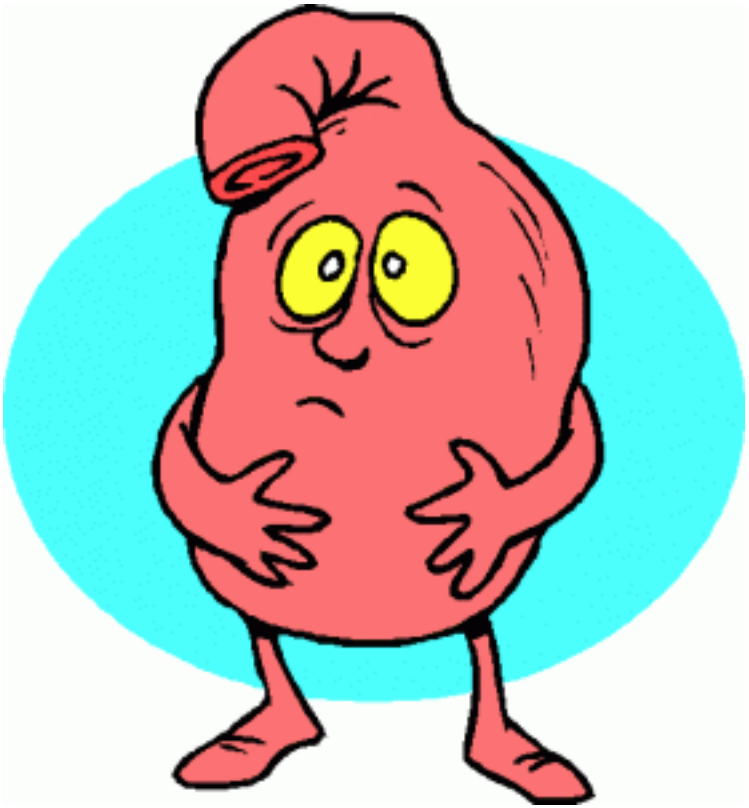
Table 1

Examples of Commonly Used Laxatives
(For directions and proper dosage, talk to your physician)

AGENT	EXAMPLES OF BRAND NAMES
Commercial Fiber Products*	
Methylcellulose	Citrucel
Psyllium	Metamucil, Konsyl
Calcium polycarbophil	Fiberall, FiberCon, Equalactin
Osmotic Laxatives	
Poorly Absorbed Ions	
Magnesium hydroxide	Uro-Mag, Milk Of Magnesia
Magnesium citrate	Citroma
Sodium phosphate	Fleet Phospho-Soda, K Phos Neutral Tablets
Poorly Absorbed Sugars	
Lactulose	Enulose, Cephulac, Kristalose, Duphalac
Polyethylene glycol	MiraLax
Sorbitol solution (70%)	Cystosol, Minilax, Resulax, Sorbilax
Stimulant Laxatives	
Anthraquinones	
Senna	Perdiem, Senokot
Ricinoleic acid	
Castor oil	
Diphenylmethane derivatives	
Bisacodyl	Dulcolax, Correctol
Emollients (Stool Softeners)	
Docusates	Colace
Mineral oil	Fleet Mineral Oil

*Take with plenty of liquids.

Lembo et al, Current Pharacologic Treatments of Irritable Bowel Syndrome, International Foundation for Functional Gastrointestinal Disorders, 2012



Lembo et al, Current Pharacologic Treatments of Irritable Bowel Syndrome, International Foundation for Functional Gastrointestinal Disorders, 2012

Table 2
Examples of Antispasmodics. (For directions and proper dosage talk to your physician.)

AGENTS	EXAMPLES OF BRAND NAME
Anticholinergics	
Dicylomine	Bentyl, Bemote
Hyoscyamine	Levsin, NuLev, Levbid
Propantheline bromide	Pro-Banthine
Mebeverine	Colofac (Australia)
Cimetropium bromide	Alginor (Italy)
Cimetropium bromide + chlordiazepoxide hydrochloride (Librium)	Librax, Clindex
Hyoscyamine +scopolamine, atropine, phenobarbital	Donnatal
Peppermint Oil	Elanco (Enteric coated), Peppermint Spirits
Direct Smooth Muscle Relaxants	
Pinaverium *	Dicetel (Canada)
Octilonium bromide *	Citanest Octapressin (Italy, Mexico, Sweden, Norway, others)
Mebeverine *	Colofac (Australia)
Trimebutine *	Modulon (Canada)
Cimetropium bromide *	Alginor (Italy)

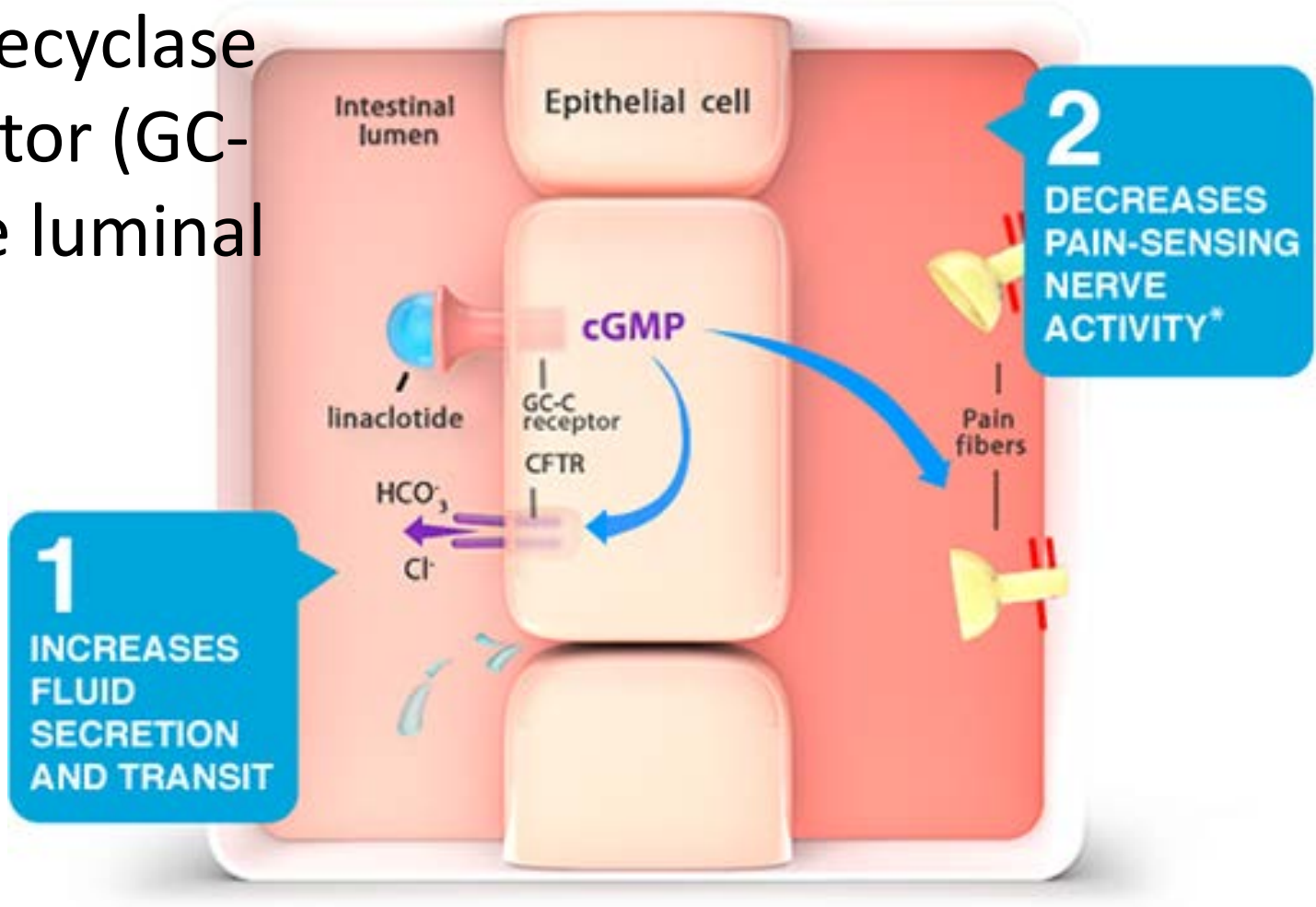
* Not available in the United States.

New Meds for IBS

- GuanylateCyclase C Agonist
  - linaclotide (Linzess)
  - Plecanatide (coming soon)
- CIC-2 Chloride Channel agonist
  - Lubiprostone (Amitiza)
- Mu-opiaid receptor agonist / delta receptor antagonist
  - Eluxadoline (coming soon)

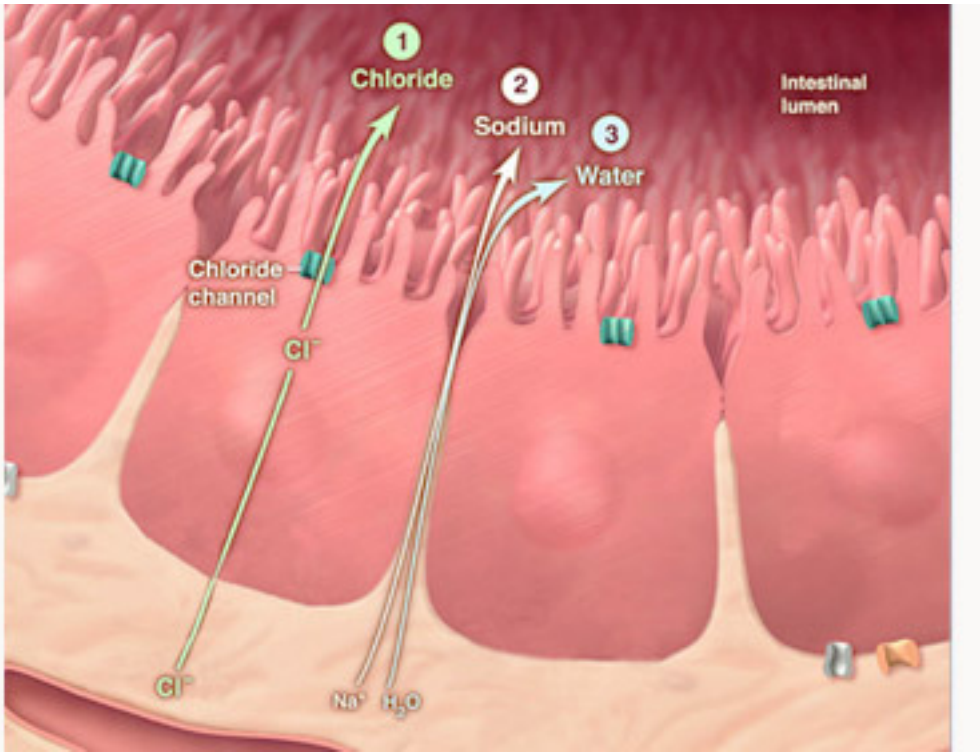
linaclotide (Linzess)

- Binds guanylatecyclase –C receptor (GC-C) on the luminal side



Lubiprostone (Amitiza)

- Activites CIC-2 chloride channels on the apical aspect of GI cell producing a chloride-rich flu secretion

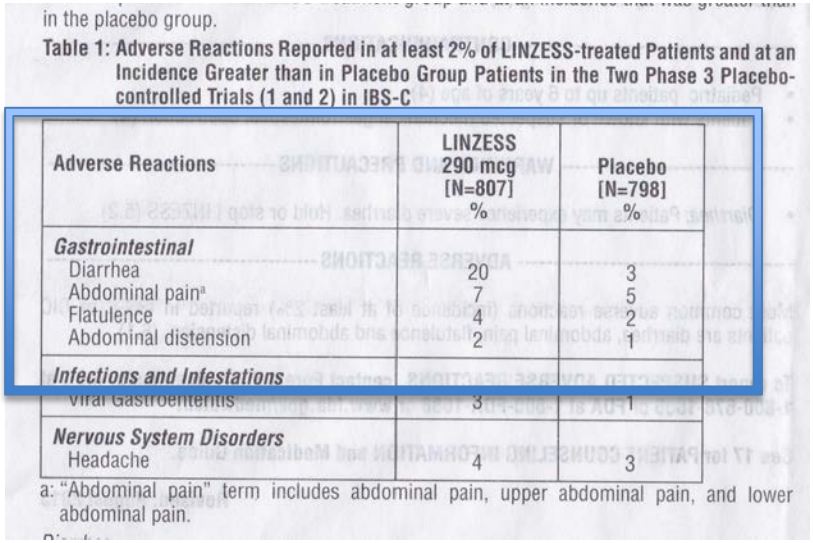


Dosing

- linaclotide (Linzess):
  - IBS-C: 290 mcg PO once daily (30 min prior to BK)
  - Chronic Constipation: 145 mcg PO once daily
- lubiprostone (Amitiza)
  - IBS-C: 8 mcg PO twice daily
  - Chronic Constipation: 24 mcg PO twice daily

linaclotide (Linzess)

Lubiprostone (Amitiza)

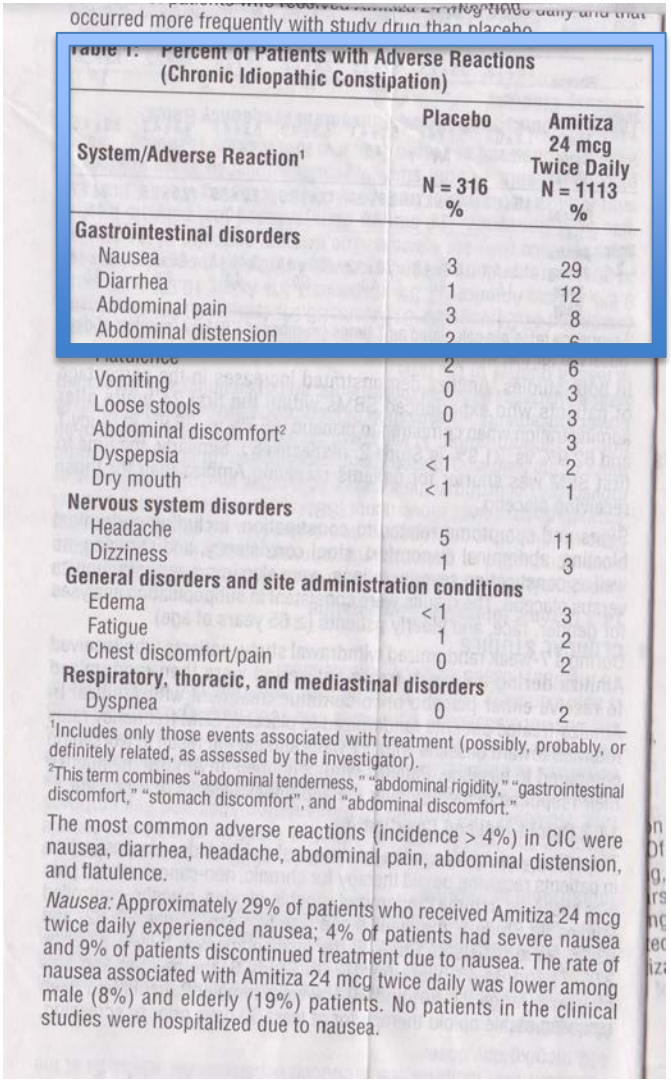


in the placebo group.

Table 1: Adverse Reactions Reported in at least 2% of LINZESS-treated Patients and at an Incidence Greater than in Placebo Group Patients in the Two Phase 3 Placebo-controlled Trials (1 and 2) in IBS-C

Adverse Reactions	LINZESS 290 mcg [N=807] %	Placebo [N=798] %
Gastrointestinal		
Diarrhea	20	3
Abdominal pain[a]	7	5
Flatulence	4	2
Abdominal distension	2	1
Infections and Infestations		
Viral Gastroenteritis	3	1
Nervous System Disorders		
Headache	4	3

a: "Abdominal pain" term includes abdominal pain, upper abdominal pain, and lower abdominal pain.



occurred more frequently with study drug than placebo.

Table 1: Percent of Patients with Adverse Reactions (Chronic Idiopathic Constipation)

System/Adverse Reaction[1]	Placebo N = 316 %	Amitiza 24 mcg Twice Daily N = 1113 %
Gastrointestinal disorders		
Nausea	3	29
Diarrhea	1	12
Abdominal pain	3	8
Abdominal distension	2	6
Flatulence	2	6
Vomiting	0	3
Loose stools	0	3
Abdominal discomfort[2]	1	3
Dyspepsia	< 1	2
Dry mouth	< 1	1
Nervous system disorders		
Headache	5	11
Dizziness	1	3
General disorders and site administration conditions		
Edema	< 1	3
Fatigue	1	2
Chest discomfort/pain	0	2
Respiratory, thoracic, and mediastinal disorders		
Dyspnea	0	2

[1]Includes only those events associated with treatment (possibly, probably, or definitely related, as assessed by the investigator).

[2]This term combines "abdominal tenderness," "abdominal rigidity," "gastrointestinal discomfort," "stomach discomfort", and "abdominal discomfort."

The most common adverse reactions (incidence > 4%) in CIC were nausea, diarrhea, headache, abdominal pain, abdominal distension, and flatulence.

Nausea: Approximately 29% of patients who received Amitiza 24 mcg twice daily experienced nausea; 4% of patients had severe nausea and 9% of patients discontinued treatment due to nausea. The rate of nausea associated with Amitiza 24 mcg twice daily was lower among male (8%) and elderly (19%) patients. No patients in the clinical studies were hospitalized due to nausea.

Both cause diarrhea, surprise!

Linaclotide high dose: 7% Abdominal Pain

Lubiprostone high dose: 29% nausea, 8% Abdominal Pain

IBS Clinical Trials (to reduce pain)
3 month trials, different definitions
Source:Both Drugs Package Inserts

linaclotide (Linzess)

- "Weekly Responder" if a 30% reduction from baseline in mean abdominal pain, at least 3 CSBM's, and increase of 1 CSBM from baseline in the same week
- Endpoints were percentage of patients who were responders
  - 9 of 12 weeks (data shown)
  - 6 of 12 weeks

Lubiprostone (Amitiza) 8 mcg BID

- "Overall Responder" if in 2 of 3 months they had:
  - "significantly relief" for at least 2 of the 4 weeks that month –OR-
  - "moderately relieved all 4 weeks that month

IBS Clinical Trials (to reduce pain)
3 month trials, different definitions
Source:Both Drugs Package Inserts

linaclotide (Linzess)

Table 3: Efficacy Responder Rates in the Two Placebo-controlled IBS-C Trials: at Least 9 Out of 12 Weeks

	Trial 1			Trial 2		
	LINZESS 290 mcg (N=405)	Placebo (N=395)	Treatment Difference [95% CI]	LINZESS 290 mcg (N=401)	Placebo (N=403)	Treatment Difference [95% CI]
Combined Responder* (Abdominal Pain and CSBM Responder)	12.1%	5.1%	7.0% [3.2%, 10.9%]	12.7%	3.0%	9.7% [6.1%, 13.4%]
Abdominal Pain Responder* (≥ 30% Abdominal Pain Reduction)	34.3%	27.1%	7.2% [0.9%, 13.6%]	38.9%	19.6%	19.3% [13.2%, 25.4%]
CSBM Responder* (≥ 3 CSBMs and Increase ≥1 CSBM from Baseline)	19.5%	6.3%	13.2% [8.6%, 17.7%]	18.0%	5.0%	13.0% [8.7%, 17.3%]

* Primary Endpoints
Note: Analyses based on first 12 weeks of treatment for both Trials 1 and 2
CI = Confidence Interval

Lubiprostone (Amitiza) 8 mcg BID

The percentage of patients in Study 1 qualifying as an "overall responder" was 13.8% in the group receiving Amitiza 8 mcg twice daily compared to 7.8% of patients receiving placebo twice daily. In Study 2, 12.1% of patients in the Amitiza 8 mcg group were "overall responders" versus 5.7% of patients in the placebo group. In both studies, the treatment differences between the placebo and Amitiza groups were statistically significant.

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Abs Risk Reduction = Experimental Rate (% of Responders) – Control Rate (%of Responders)

Linaclotide:
Trial 1: 34.3% - 27.1% = 7.2%

Trial 2: 38.9%-19.6% =19.3%

Lubiprostone:
Trial 1: 13.8% - 7.8% = 6%
Trial 2: 12.1% - 5.7% = 6.4%

IBS Clinical Trials (to reduce pain)
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linaclotide (Linzess)

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Acknowledgement: The definitions were different, which may be apparent by the dramatically different placebo response rates!

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Number Needed to Treat = 1 / (EER-CER)

Linaclotide:

Trial 1: 34.3% - 27.1% = 7.2% → 13.8

Trial 2: 38.9%-19.6% =19.3% → 5.1

Lubiprostone:

Trial 1: 13.8% - 7.8% = 6% → 16.6

Trial 2: 12.1% - 5.7% = 6.4% → 15.6

Dig Dis Sci (2013) 58:2580–2586
DOI 10.1007/s10620-013-2684-z

ORIGINAL ARTICLE

Plecanatide, an Oral Guanylate Cyclase C Agonist Acting Locally in the Gastrointestinal Tract, Is Safe and Well-Tolerated in Single Doses

Kunwar Shailubhai · Stephen Comiskey · John A. Foss · Rong Feng · Laura Barrow · Gail M. Comer · Gary S. Jacob

GASTROENTEROLOGY 2013;145:329–338

Eluxadoline Benefits Patients With Irritable Bowel Syndrome With Diarrhea in a Phase 2 Study

LEONARD S. DOVE,[1] ANTHONY LEMBO,[2] CHARLES W. RANDALL,[3,4] RONALD FOGEL,[5] DAVID ANDRAE,[1] J. MICHAEL DAVENPORT,[1] GAIL MCINTYRE,[1] JUNE S. ALMENOFF,[1] and PAUL S. COVINGTON[1]

[1]Furiex Pharmaceuticals, Morrisville, North Carolina; [2]Harvard Medical School, Center for Clinical and Translational Research in Gastrointestinal Motility, Beth Israel Deaconess Medical Center, Division of Gastroenterology, Boston, Massachusetts; [3]University of Texas Health Science Center, San Antonio, Texas; [4]Gastroenterology Research of America, San Antonio, Texas, and [5]Digestive Health Centers of Michigan, Chesterfield, Michigan

- Mu-opioid receptor agonist and delta opioid receptor antagonist
- Reduces GI transit and fecal output in stressed and nonstressed mice
- While imodium prevents fecal output in a dose-dependent manner, this doesn’t

- Primary end point: Percentage of patients who achieved clinical response at week 4 defined:
  - Decrease in daily Worse Abdominal Pain scores from baseline by 30% -AND-
  - At least 2 points and a daily Bristol Stool Scale score of 3 or 4 on >/= 66% of daily entries within that week

Table 2. Primary and Secondary Efficacy Results: Clinical Response Criteria (Intent-to-Treat Population)

	Eluxadoline				
	5 mg (n = 105)	25 mg (n = 167)	100 mg (n = 163)	200 mg (n = 160)	Placebo (n = 159)
Primary end point					
Clinical response					
Week 4					
Composite, %	12.4[a]	12.0[b]	11.0[a]	13.8[b]	5.7
OR (95% CI)	2.46 (0.99–6.08)	2.38 (1.04–5.48)	2.08 (0.89–4.84)	2.80 (1.23–6.38)	
Abdominal pain, %	39.0	40.7	39.3	39.4	39.6
OR (95% CI)	1.06 (0.62–1.81)	1.08 (0.67–1.72)	0.99 (0.62–1.60)	1.02 (0.64–1.64)	
Stool consistency, %	12.4	16.8[b]	14.1[a]	18.1[b]	8.2
OR (95% CI)	1.58 (0.70–3.58)	2.38 (1.18–4.80)	1.90 (0.92–3.92)	2.61 (1.29–5.26)	

B= $p<0.05$ compared to placebo

GASTROENTEROLOGY 2013;145:320–328

No Effects of Gluten in Patients With Self-Reported Non-Celiac Gluten Sensitivity After Dietary Reduction of Fermentable, Poorly Absorbed, Short-Chain Carbohydrates

JESSICA R. BIESIEKIERSKI,[1,2] SIMONE L. PETERS,[2] EVAN D. NEWNHAM,[1] OURANIA ROSELLA,[2] JANE G. MUIR,[2] and PETER R. GIBSON[2]

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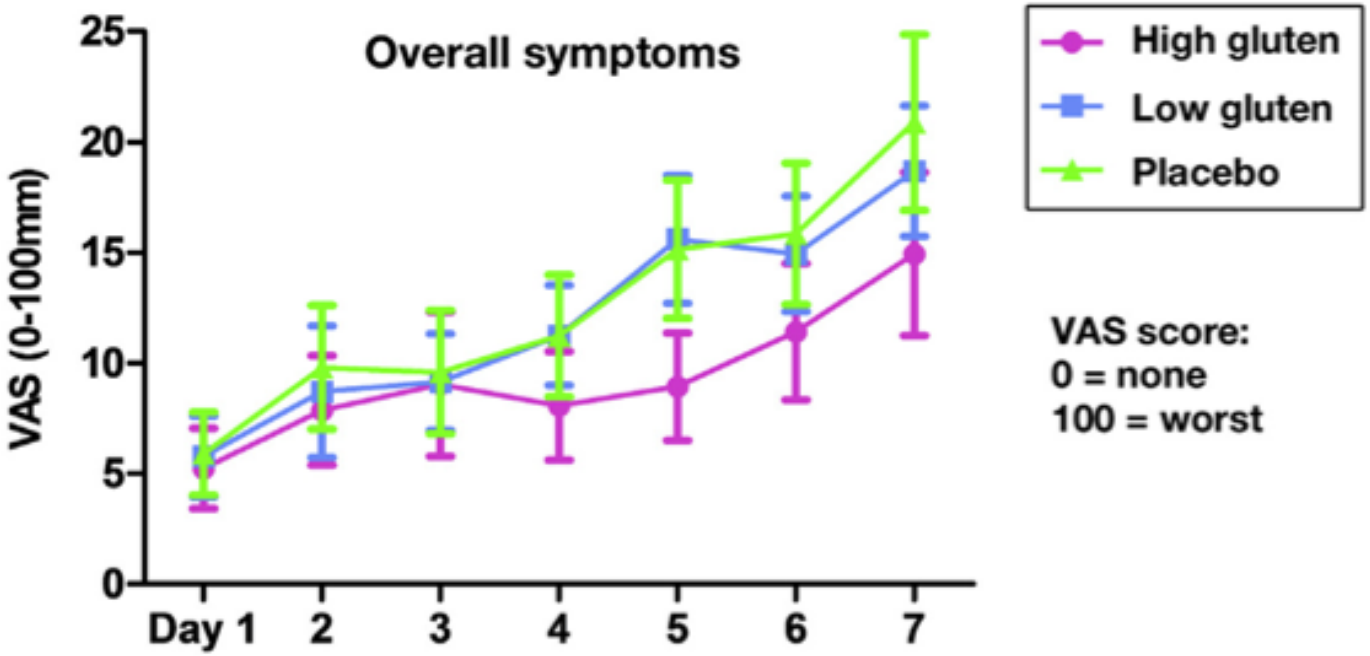

Gastroenterology 2014;146:67–75

CLINICAL—ALIMENTARY TRACT

A Diet Low in FODMAPs Reduces Symptoms of Irritable Bowel Syndrome

Emma P. Halmos,[1,2] Victoria A. Power,[1] Susan J. Shepherd,[1] Peter R. Gibson,[1,2] and Jane G. Muir[1,2]

[1]Department of Medicine, Eastern Health Clinical School, Monash University, Box Hill, Victoria, Australia; [2]Department of Gastroenterology, Central Clinical School, Monash University, Melbourne, Victoria, Australia

-30 patients with IBS and 8 healthy individuals (controls, matched for demographics and diet)
-Dietary data from subjects for 1 habitual week.

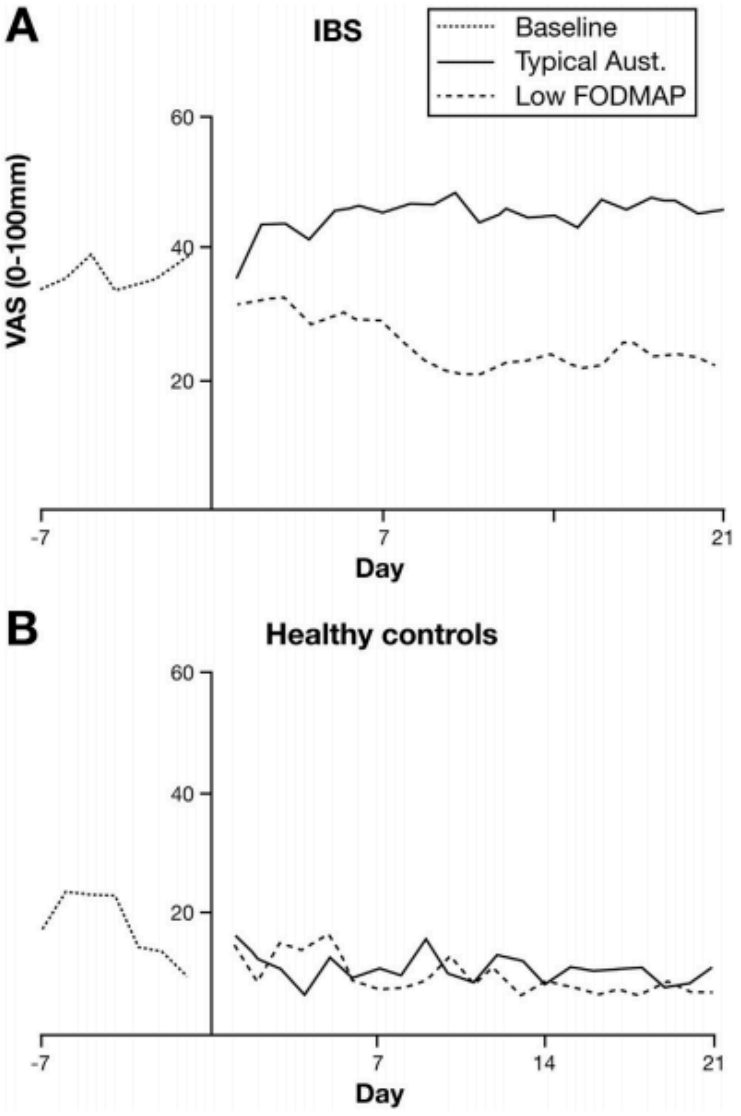

Figure 1. Mean overall gastrointestinal symptoms from the (*A*) IBS cohort and the (*B*) healthy cohort using a VAS during baseline, low FODMAP and typical Australian diets. Symptoms improved significantly on low FODMAP compared with baseline and the typical Australian diet for the IBS cohort. No differences were observed between any of the diets in the healthy cohort.

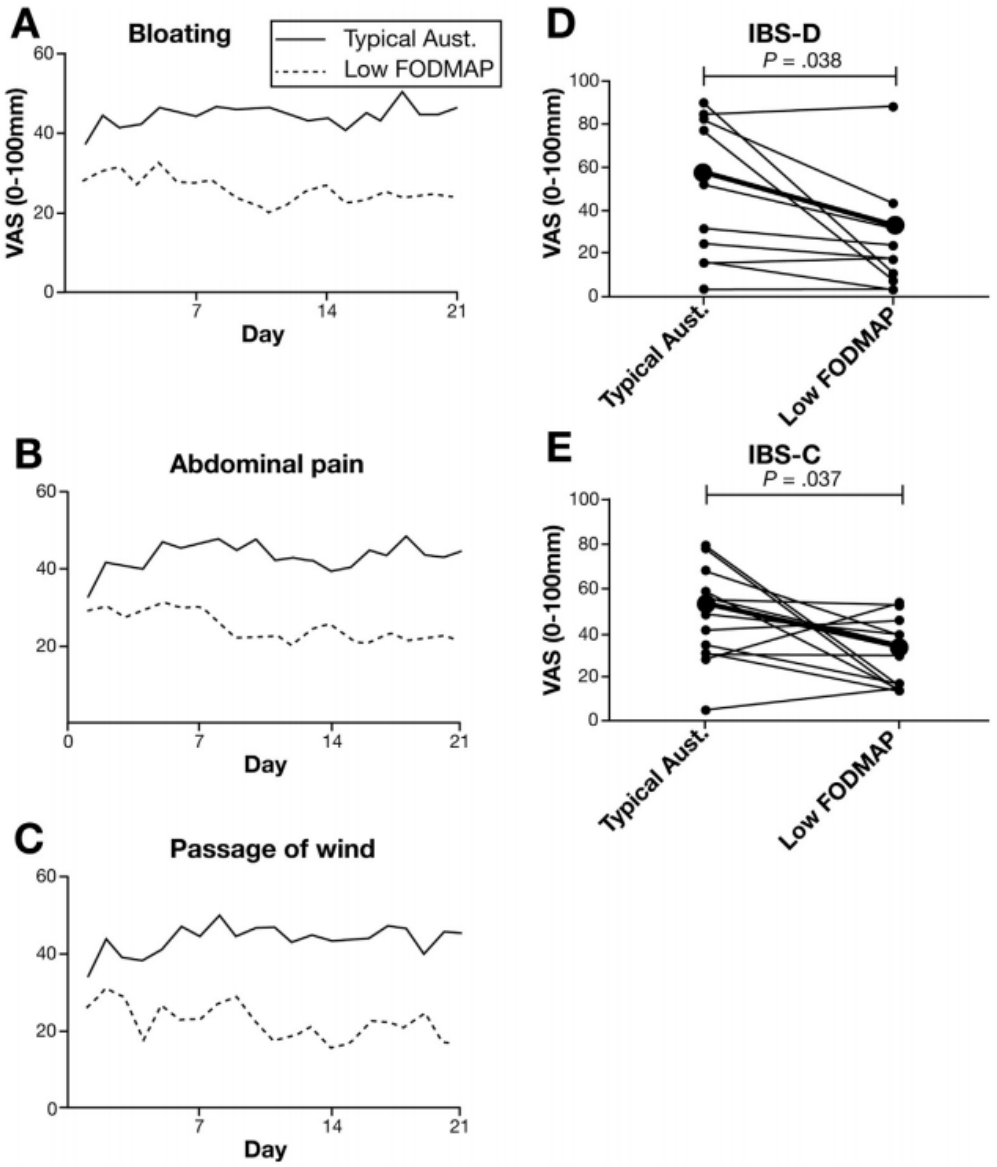

Table 3. Bloating, Abdominal Pain, Dissatisfaction With Stool Consistency, and Composite Scores of All Three Symptoms in IBS and Healthy Participants While Following Low FODMAP and Typical Australian Diets

		Bloating		Abdominal pain		Dissatisfaction with stool consistency		Composite scores	
Subject group	Diet	VAS (0–100 mm)						VAS (0–300 mm)	
IBS (n = 30)	Typical Australian	**45.1 (35.1–55.0)**	***P* < .001**	**43.8 (35.0–52.5)**	***P* < .001**	**47.8 (37.6–57.9)**	***P* < .001**	**137 (110–163)**	***P* < .001**
	Low FODMAP	**24.2 (17.1–31.2)**		**22.5 (16.3–28.6)**		**25.9 (18.9–32.9)**		**73.1 (54.0–92.1)**	
Healthy controls (n = 8)	Typical Australian	11.8 (5.9–17.8)	*P* = .742	9.6 (5.1–14.4)	*P* = .742	17.7 (7.5–27.9)	*P* = .547	38.7 (19.4–57.9)	*P* = .304
	Low FODMAP	10.4 (5.4–15.4)		9.1 (4.6–13.7)		10.1 (4.9–15.2)		29.6 (14.9–44.4)	

NOTE. Data from the last 14 days of the interventional diets were analyzed using repeated-measures analysis of variance. Statistically significant differences are shown in bold.

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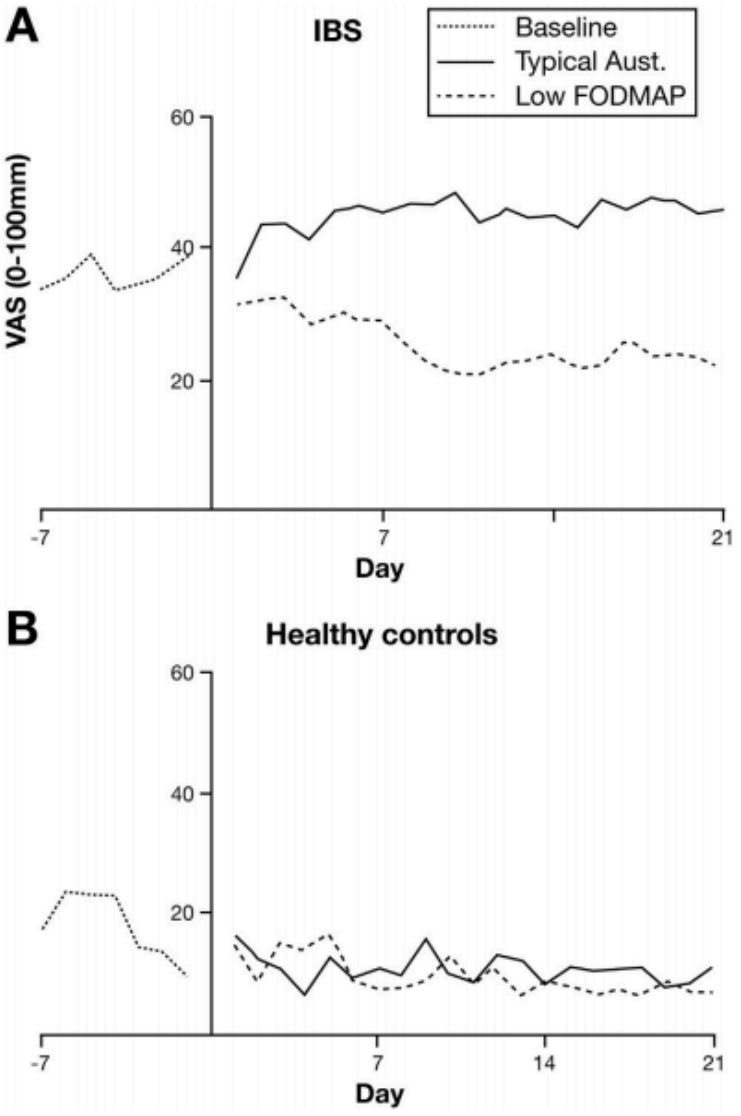

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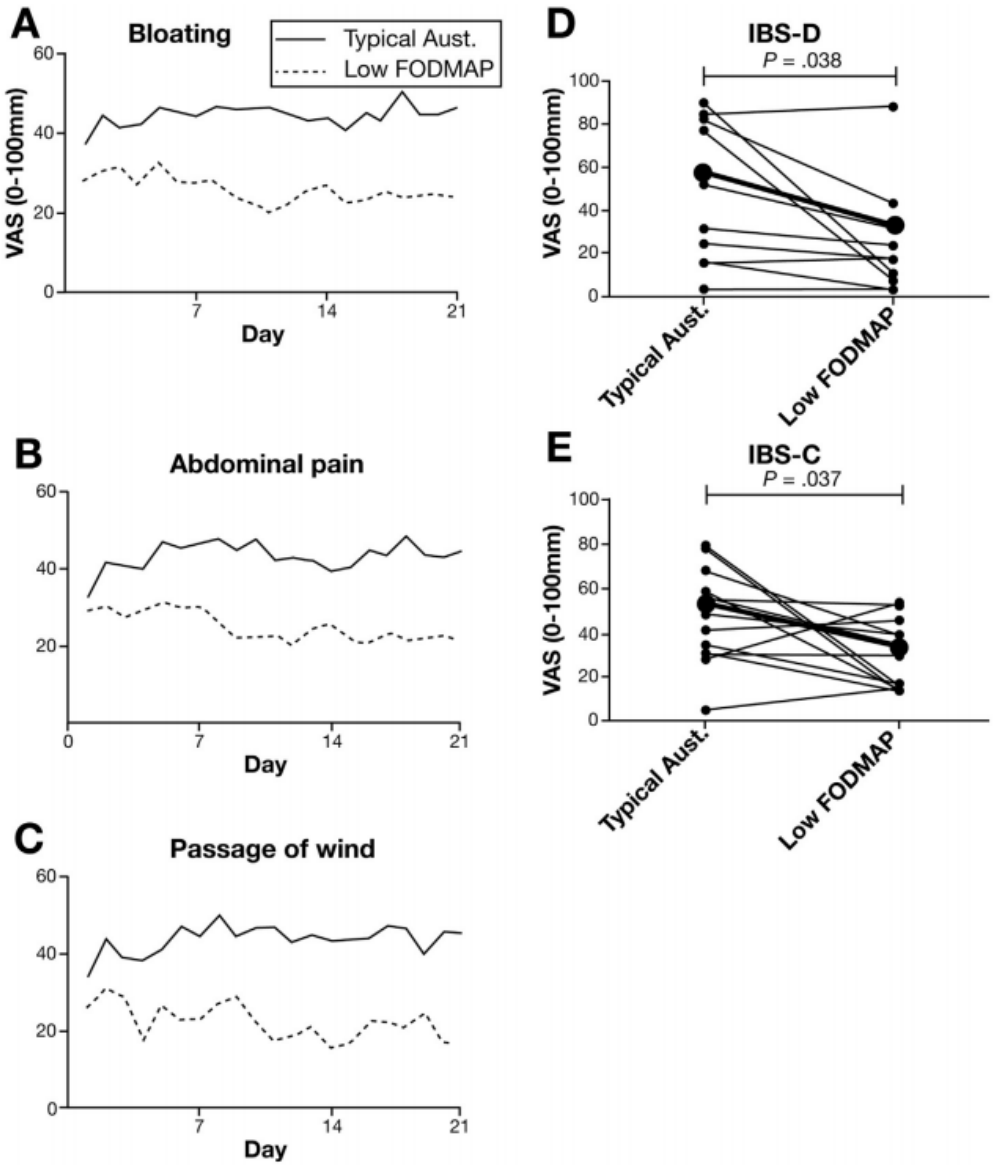

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Behaviour Research and Therapy 49 (2011) 413–421

Contents lists available at ScienceDirect

Behaviour Research and Therapy

journal homepage: www.elsevier.com/locate/brat

A cognitive-behavioral treatment for irritable bowel syndrome using interoceptive exposure to visceral sensations

Michelle G. Craske, Kate B. Wolitzky-Taylor, Jennifer Labus, Stephen Wu, Michael Frese, Emeran A. Mayer, Bruce D. Naliboff*

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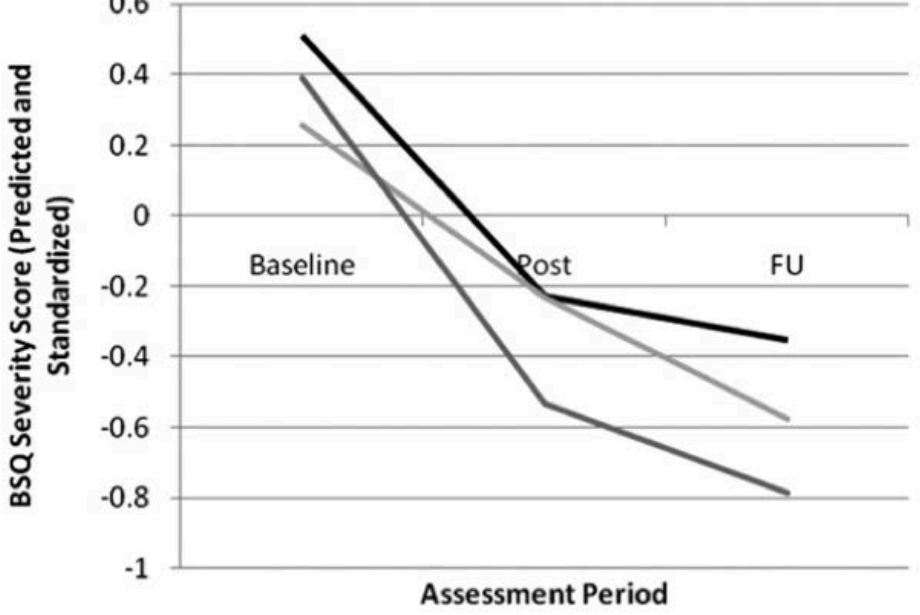

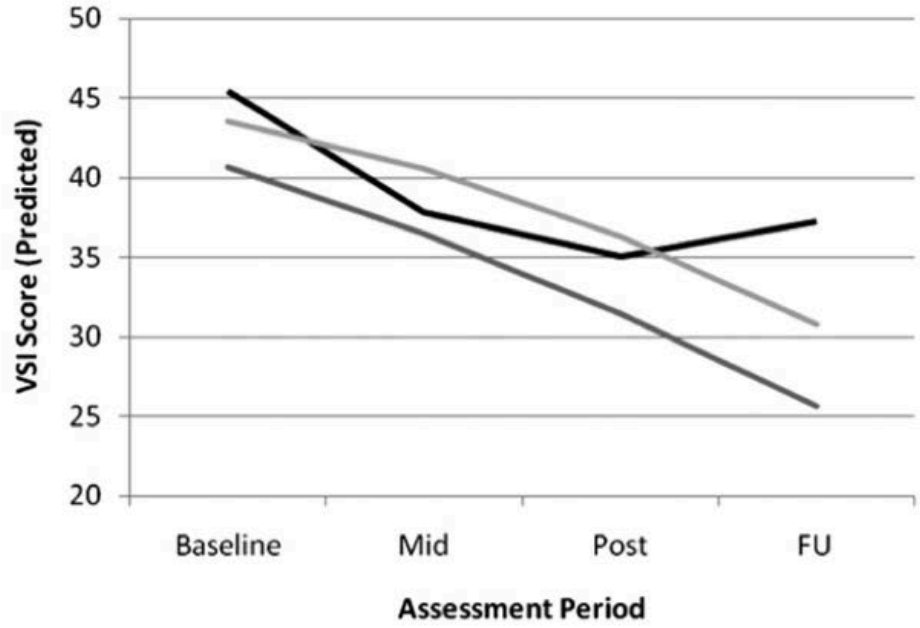

CBT- Attention Control Condition (AC)
-Self monitoring IBS symptoms
-Receiving and reading educational material
-Discussing the reading material with a therapist

CBT- stress management (SM)
-Education about IBS
-Self monitoring symptoms
-Progressive muscle relaxation
-Exposure to stressful situations (a conflict) not directly related to IBS

CBT- Interoceptive Exposure (IE)
-Target Erroneous beliefs
-Repeated exposure to tightening stomach such as tight clothing, delayed entrance to the bathroom, eating feared foods

Fig. 2. BSI decline slopes and VSI decline slopes for all three treatment groups across all assessment periods (baseline through follow-up).

Let's discuss our IBS…
Questions?