

Irritable Bowel Syndrome for Primary Care: 2021

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Learning Objectives

- At the conclusion of this session, participants should be able to:
- Identify the diagnostic criteria and symptoms of Irritable Bowel Syndrome (IBS)
- Review the differential diagnoses of patients with similar symptoms of IBS and how best to rule in IBS
- Develop evidence-based treatment plans for IBS including dietary, lifestyle modifications, non-pharmacologic, and the latest pharmacologic therapies

Defining and Characterizing IBS

Rome IV Criteria for IBS¹

Recurrent **abdominal pain**, on average, ≥ 1 day per week in the last 3 months, associated with ≥ 2 of the following:

- Related to defecation
- Change in frequency of stool
- Change in form (appearance) of stool

Criteria should be fulfilled for the last 3 months with symptom onset ≥ 6 months before diagnosis

IBS Subtypes Based on Bristol Stool Forms^{2,3}



IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrheal IBS-M, irritable bowel syndrome with mixed symptoms.
1. Lacy BE et al. *Gastroenterology*. 2016;150:1393-1407. 2. Longstreth GF et al. *Gastroenterology*. 2006;130:1480-1491.
3. O' Donnell LJD, et al. *BMJ*. 1990;300:439-440.

IBS is Common

- 10%-15% of adults in the United States report symptoms consistent with IBS
- Most common GI diagnosis among gastroenterology practices in the United States
- A top 10 reason for family clinician visits
- Prevalence:
 - S.America 21%
 - SE Asia 7%
 - Women: Men 1.5-2.0:1.0 N. America
 - Women: Men 1.0-1.0 Asia

IBS Sub-types

- IBS-C
 - Constipation predominant
 - 33-50% of IBS patients
- IBS-D
 - Diarrhea predominant, ~33% of IBS patients
- IBS-A
 - Alternating diarrhea and constipation
 - 33% of IBS patients
 - Longstreth, et al. Gastroenterol, 2006;130: 1450

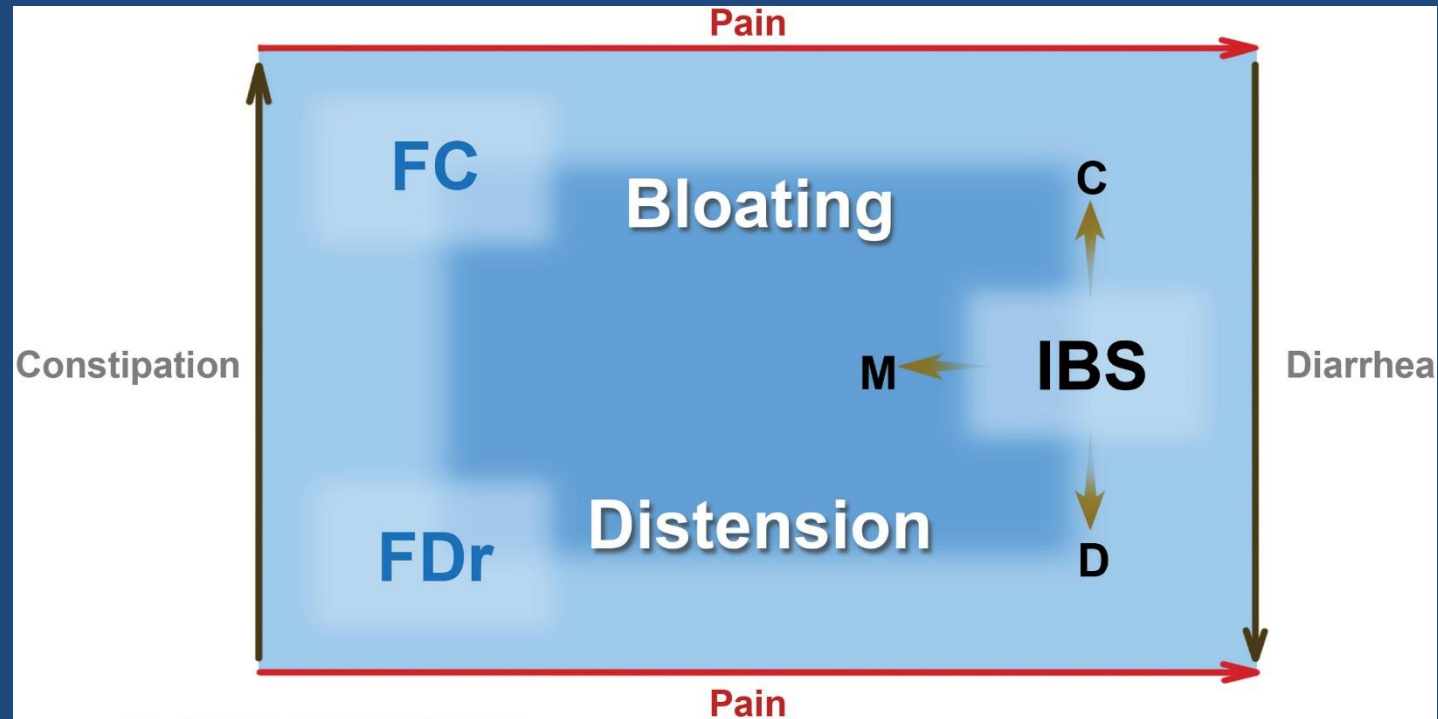
IBS-C vs Chronic Constipation

- Abdominal pain major discriminating feature
- IBS-C:
 - Elevated pain scores
 - Marked effect on activities of daily living
 - Increased healthcare utilization
 - Lower education

Drossman et al. Gastroenterol 2008;42: 1080

Rome IV: Functional Bowel Disorders

Gastroenterol 2016;150: 1393-1407



FC: Functional constipation

FDr: Functional diarrhea

IBS-C: Irritable bowel syndrome with predominant constipation

IBS-D: Irritable bowel syndrome with predominant diarrhea

IBS-M: Irritable bowel syndrome with predominant irregular bowel habits (mixed D/C)

IBS: Proposed Etiologies

Camilleri M, Clin Pharm Ther 2012;91: 44-59

Chey, W, JAMA 2015;313: 949-58

- **Environmental:**

- Early life stressors
- Food intolerance
- Antibiotics
- Enteric infection

Luminal:

- Dysbiosis
- Neuroendocrine mediators
- Bile acids

- **Host Factors:**

- Altered motility
- Visceral hypersensitivity
- Increased intestinal permeability
- Mast cell activation with histamines, tryptase release

IBS-History

- Change in bowel habits, frequency, stool consistency
- Duration of symptoms? Precipitating factors?
- Abdominal pain, bloating, when, where?
- Associated symptoms?
- Association with meals?
- Recent illness prior to onset of symptoms
- Family history of similar symptoms?

IBS: History (cont.)

- **Pregnancy?**
- **Excessive pain or bleeding?**
- **History of physical or sexual abuse**
- **History of eating disorder?**
- **Post-traumatic stress disorder (men&women)?**








Chang, L et al. Gastroenterol, 2002;123: 1686

History: Alarm Features

- Onset after age 50, or an acute or gradual onset in elderly patients
- Hx of Anemia/Fe deficiency
- Unintentional weight loss
- Family history of colon cancer, other GI malignancy, or IBD
- Nocturnal symptoms
- Fever
- Oral aphthous ulcers
- Hematochezia
- Ophthalmic inflammation (iritis/scleritis)
- Dermatologic conditions e.g. erythema nodosum, pyoderma gangrenosum
- Inflammatory arthritis

Whitehead et al. Aliment Pharmacol Ther 2006;24: 137

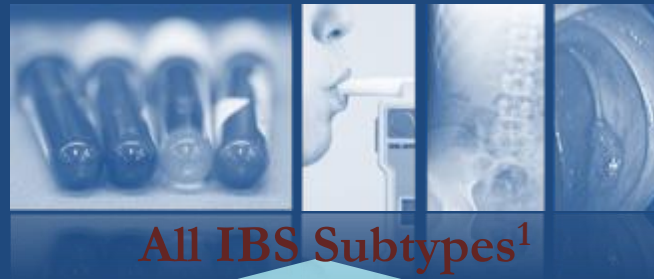
Bristol Stool Form Scale

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 its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces Entirely liquid

Focused Physical Exam

- Abdominal examination
- Digital rectal examination and perineal inspection
- Pelvic examination, when indicated
- Assessment of neurologic function (anocutaneous reflex, DTRs lower ext)

Diagnostic Testing for Patients with Suspected IBS and No Concerning* Features



All IBS Subtypes¹

CBC

Age-appropriate CRC screening

IBS-D^{1,2}

- CRP or fecal calprotectin
- IgA TtG ± quantitative IgA
- When colonoscopy performed, obtain random biopsies
- SeHCAT, fecal bile acids, or serum C₄ where available
- Anti-CdtB/anti-vinculin antibodies²

IBS-M¹

- CRP or fecal calprotectin
- IgA TtG ± quantitative IgA
- Stool diary
- Consider abdominal plain film to assess for fecal loading

IBS-C¹

If severe or medically refractory, refer to specialist for physiologic testing

***Alarm features** include age ≥50 years old, blood in stools, nocturnal symptoms, unintentional weight loss, change in symptoms, recent antibiotic use, and family history of organic GI disease. C₄, 7 α -hydroxy-4-cholesten-3-one; CBC, complete blood count; CRC, colorectal screening; CRP, C-reactive protein; SeHCAT, selenium homocholic acid taurine; TtG, tissue transglutininase.

1. Chey WD et al. *JAMA*. 2015;313(9):949-958. 2. Pimentel M et al. *PLoS ONE*. 2015;10(5):e0126438.

Case #1: Sam

- 28 y/o wm surgical resident
- Bilateral lower abdominal aching pain if no bm that day with associated bloating/distention
- Hard to pellet-like stools every 2-3 days with relief of abdominal discomfort; no rectal bleeding
- No weight loss, fevers, rash, arthralgias, N or V
- Onset of sx as undergrad, worse during residency, long hrs in OR, and when giving case conference presentations

Case #1 (cont'd)

- PMH: seasonal allergies; no previous surgeries
- SH: single, non-smoker, occasional beer

PE: WD/WN in nad; VSS

Abd: normal BS, no HSM, soft with mild LLQ tenderness; no palpable masses/fullness

Normal perianal inspection and DRE, heme (-)

Labs: CBC, CMP, TSH, normal

Case #1 (cont'd)

- What differentiates his symptoms from chronic constipation vs IBS-C?
- Further testing or treat with confidence?
- First line treatment choices?
- Dietary modification?

Searching for IBS-C/CIC: Differential Diagnoses

Chronic idiopathic constipation

IBS-C

Medication-induced constipation
(NSAIDs, narcotics, antacids,
bile acid sequestrants, anticholinergics)

Dyssynergic defecation

Pelvic floor dysfunction

Slow transit constipation



Differentiating CIC from IBS-C: Rome IV Diagnostic Criteria

IBS

Recurrent abdominal pain, on average, ≥ 1 day per week in the last 3 months, associated with ≥ 2 of the following:

- Related to defecation
- Change in frequency of stool
- Change in form (appearance) of stool

Criteria should be fulfilled for the last 3 months with symptom onset ≥ 6 months before diagnosis.

Functional constipation

Must include ≥ 2 of the following:

- Straining
- Lumpy or hard stools (BSFS 1-2)
- Sensation of incomplete evacuation
- Sensation of anorectal obstruction/blockage
- Manual maneuvers to facilitate $>25\%$ defecations
- <3 SBMs per week

$>25\%$ of defecations

Criteria should be fulfilled for the last 3 months with symptom onset ≥ 6 months before diagnosis. Loose stools are rarely present without the use of laxatives. Insufficient criteria for IBS.

IBS-C Therapies

IBS: Non-Pharmacologic Treatments

- Behavioral modification
 - Relaxation techniques
 - Biofeedback
 - Hypnosis
- Cognitive behavioral therapy
 - Coping with chronic illness and stress
 - Treating concomitant anxiety, depression

Lackner JM, et al, Gastroenterol 2007;133: 433-44

IBS: Therapies

Anti-spasmodic Medications

- Dicyclomine, Hyoscyamine
- May decrease pain of colonic spasm
- May worsen constipation
- Insufficient data in IBS-C

ACG Task Force, Am J Gastroenterol 2002;97: 51

Selective Serotonin Reuptake Inhibitors

- Serotonin and its receptors influence gastrointestinal motility and hypersensitivity
- > 90% of serotonin content within the gut
- Serotonin predominantly in the enterochromaffin (EC) cells of enteric nervous system
- Agents include fluoxetine, citalopram, and paroxetine
- Helpful for treatment of underlying depression but not of IBS symptoms

Wald A, J Clin Gastroenterol 2002;35(suppl): S53.

IBS:

Tricyclic Antidepressants

- E.g. Amitriptyline, nortriptyline
- No better than placebo at relieving global IBS symptoms
- May improve diarrhea and abdominal pain of IBS
- May worsen constipation

ACG Task Force, Am J Gastroenterol 2002;97: 81

Bulking Agents and Stool Softeners

- Bulking agents increase volume of stool
- Psyllium (*Ispaghula husk*)
 - Bloating is common adverse event
 - Potential allergic reaction in some patients
- Stool softeners (e.g, docusate sodium)
 - Efficacy in IBS not well established
 - May inhibit fluid absorption

Quartero AO et al.,Cochrane Database Syst Rev.2005;(2):
CD003460.

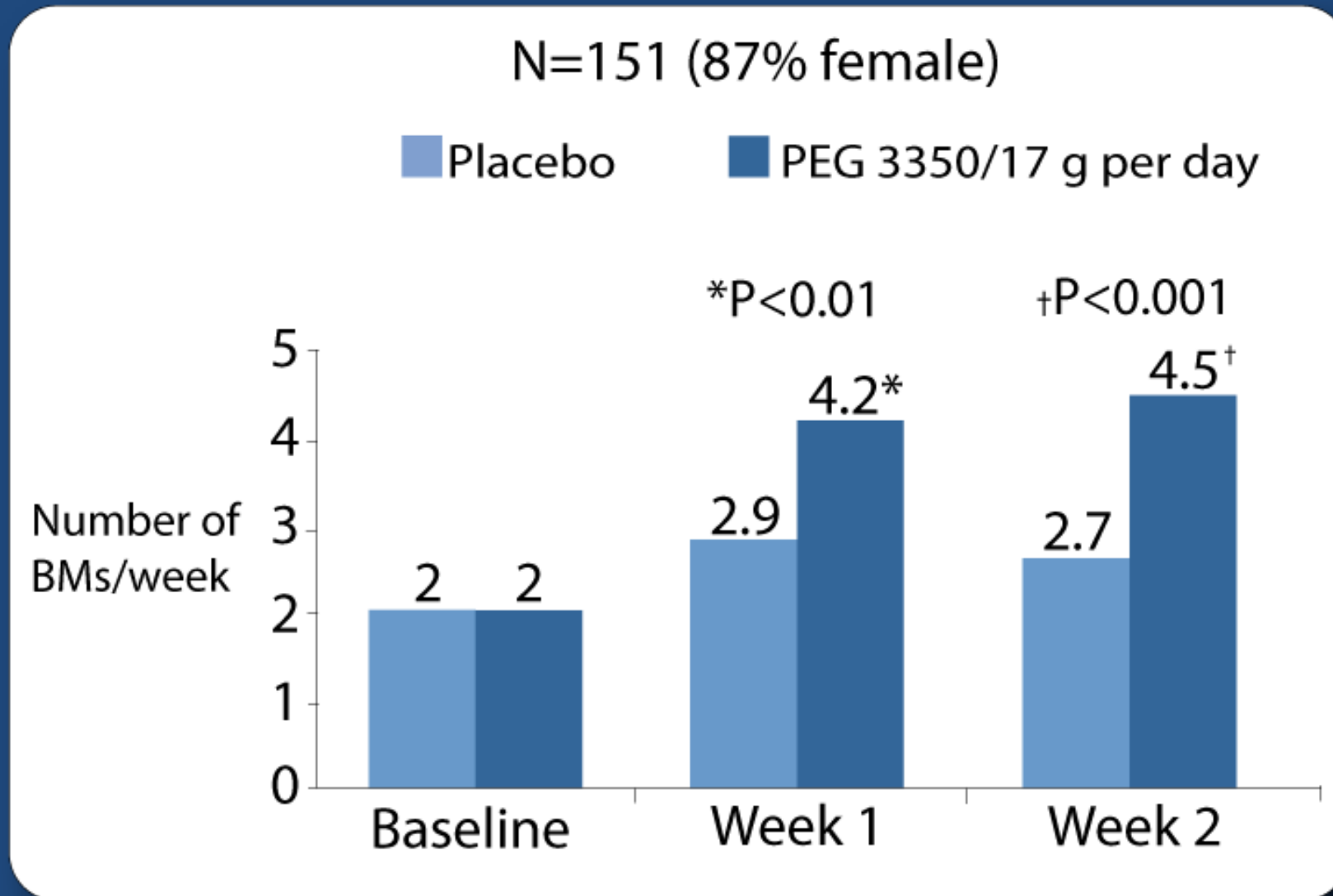
IBS-C Therapy: Osmotic Laxatives, *Lactulose*

- Osmotic laxatives improve constipation by pulling fluid into the colon lumen
- Evidence is lacking for efficacy and tolerability in IBS
- Lactulose
 - Typical dose is 15 ml/10 gm to 30 ml/20 gm / day
 - Common adverse effects of flatulence and intestinal cramps
 - Tack J, Aliment Pharmacol Ther 2006;24: 183

IBS-C Interventions – Osmotic Laxatives

Polyethylene glycol (PEG)

DiPalma et al. Am J Gastro 2000;95: 446



IBS-C Therapy:

Lubiprostone

- Selective chloride-channel receptor agonist (ClC-2)
 - Enhances intestinal fluid secretion without altering serum electrolyte levels
- Approved in US for treatment of chronic constipation 2006 and IBS-C adult females in 2008

Johanson JF, et al, Gastroenterol 2006;130(suppl2): A25

IBS-C Therapy: Lubiprostone

- Starting dose 8 mcg capsules BID *with* food on an empty stomach
- Increased number of bm/wk and decreased abdominal pain/discomfort
- Common adverse effects: diarrhea and nausea
- Gastroenterol 2006;130 (suppl 2): A25

IBS-C Therapy: Linaclotide

- Guanylate cyclase-C agonist
- FDA-approved 2012 for CC and IBS-C in adults only >18 yrs
- Increases intestinal water and electrolyte secretion
- Accelerates ascending colon transit

Camilleri M, Clin Pharmacol Ther 2012;91: 44-59

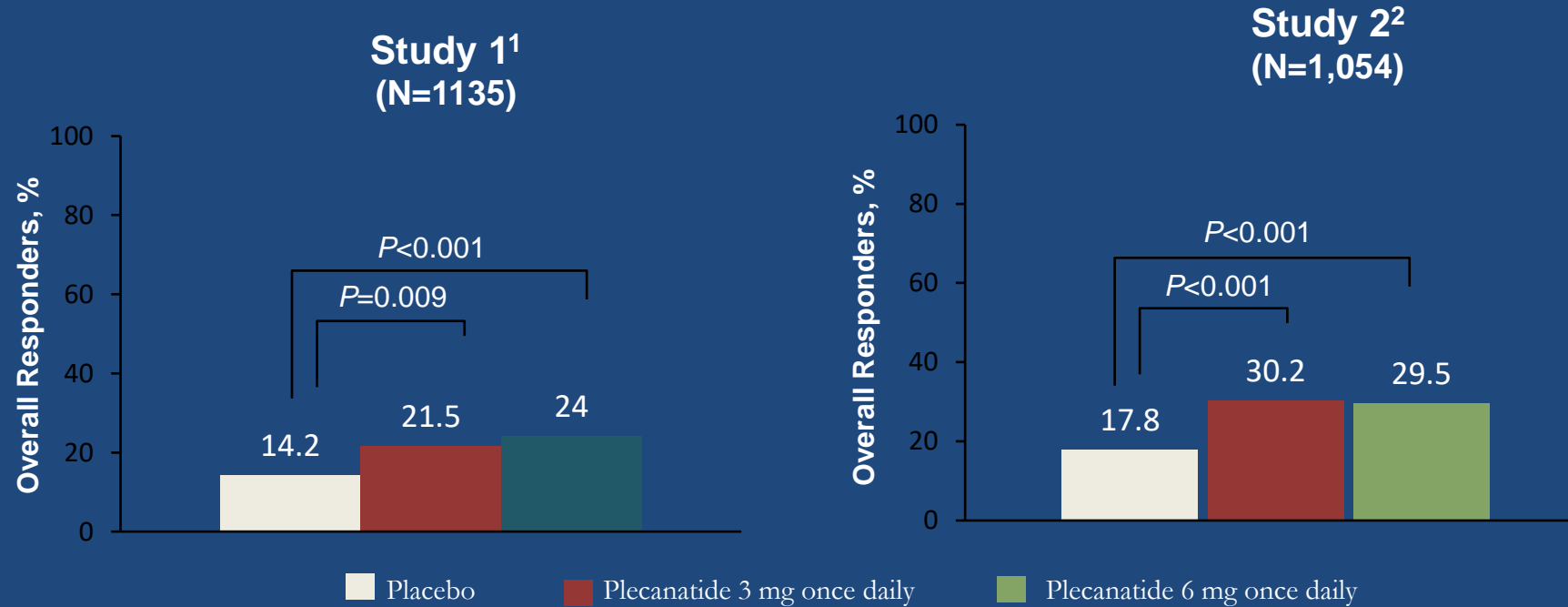
IBS-C Therapy: Linaclotide

- Improved abdominal pain and bowel movement frequency
- Diarrhea most common AE
- IBS-C dose = 290 mcg > 30 min before first meal
- CC dose = 145 mcg qd (290 dose no better than 145 in trials for CC); (now also 72 mcg dose)

Johnston JM, Gastroenterol, 139: 1877-86, 2010

Plecanatide for IBS-C: (Guanylate cyclase-C agonist)

Overall Responders During 12 Weeks* Phase 3 clinical trial



*Defined as a patient who fulfills both $\geq 30\%$ reduction in worst abdominal pain and an increase of ≥ 1 CSBM from baseline, in the same week, for $\geq 50\%$ of the 12 treatment weeks.

Brenner DM et al. *Am J Gastroenterol.* 2018;113(5):735-745.

5HT-4 Receptor Agonists

- Tegaserod: approved for IBS-C in women < 65 y/o
 - Caution in patients with C-V disease/arrhythmias, h/o ischemic colitis
 - Prucalopride: (approved for CIC 2018, not IBS-C yet)
 - Caution in patients with depression/suicidal ideation
- Stimulate intrinsic cholinergic neurons to enhance motility
- Accelerates colon transit

Camilleri M, Aliment Pharmacol Ther 2009;31: 35.

Overview of IBS-C Therapies: Mechanisms of Action

Prosecretory Agents

Lubiprostone*
Linaclotide†
Plecanatide†

Fiber/Bulking Agents‡

Stimulant Laxatives

Bisacodyl‡

Osmotic Laxatives

Polyethylene glycol



Antidepressants
SSRIs¶

*FDA-approved for CIC in adults and IBS-C in women ≥ 18 years of age; †FDA-approved for CIC and IBS-C; ‡Approved for occasional constipation; ¶Not FDA-approved for CIC or IBS-C.

IBS-C Treatment

- Psyllium offers modest clinical benefits
- PEG improves constipation but not abdominal pain or bloating in IBS
- High-quality evidence supports the efficacy of lubiprostone, linaclotide, plecanatide, and tegaserod in IBS-C
 - These agents improve abdominal and bowel symptoms
 - Curr Gastroenterol Rep 2019 21(6): 25.

IBS-D

Case #2

Ella

- 22 y/o HF graduate student with chronic intermittent diarrhea past 18 mos
- Sx onset during spring break cruise when she & several fellow passengers developed acute nausea, vomiting, and diarrhea. After IVF hydration, N&V resolved after 72h but change in bowel habits from a formed/hard stool q 2-3 d w/o discomfort to 3-4 loose stools/d, especially pc with some urgency , no blood

Case #2

Ella (cont'd)

- She also notes bilateral lower abdominal discomfort mildly relieved with a bm; weight stable. Sx worse before exams, eating out
- PMH: normal menses; no prev surg.
- SH: sgl, grad student; non-smoker, occas wine
- PE: WD/WN in nad; VSS

Abd: normal BS, no HSM; soft with mild tenderness to light palpation lower quads. Normal perianal inspect. and DRE

Case #2

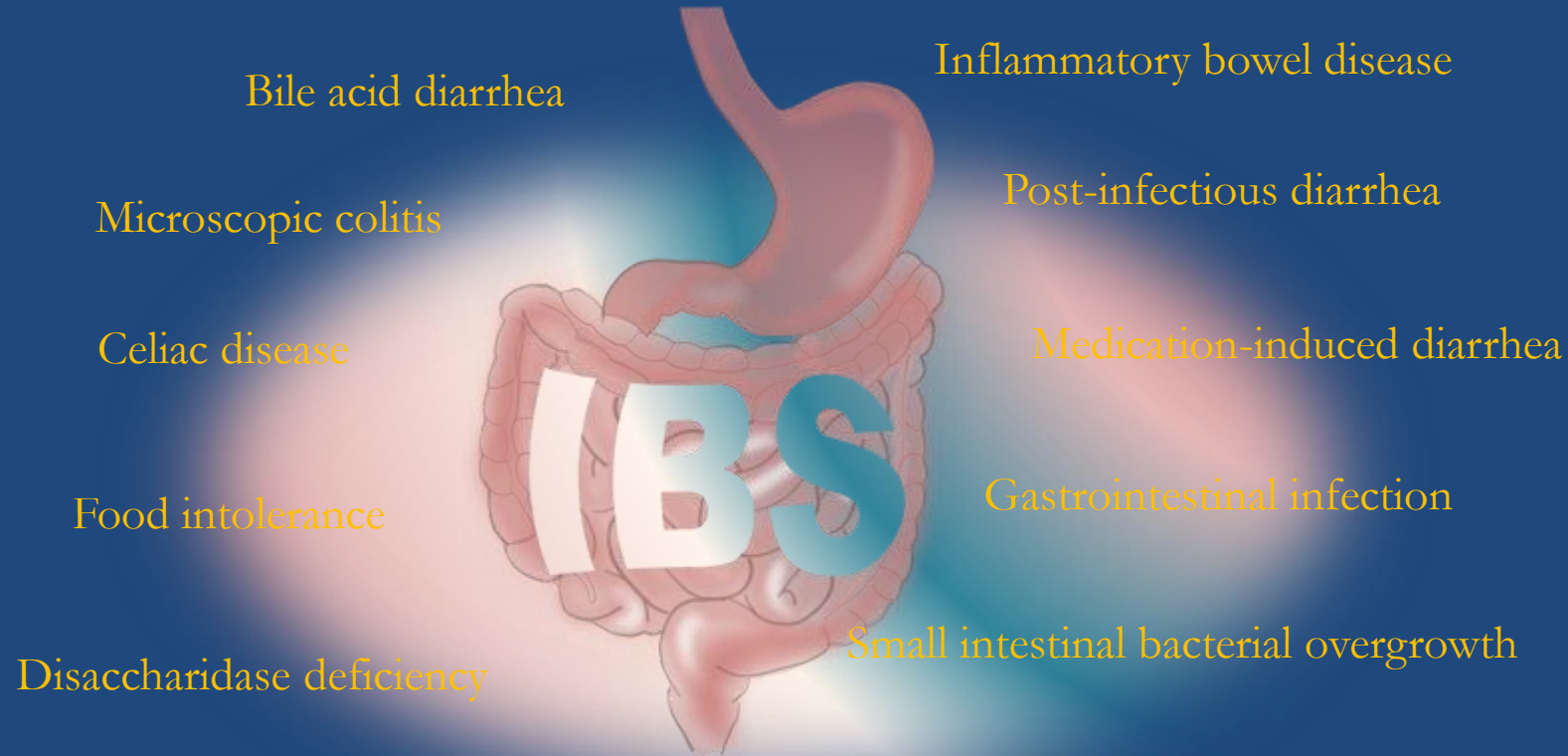
Ella (cont'd)

- Previous evaluation:
- Stool studies repeated past 6 mos and neg for enteric pathogens, O&P, protozoa, hemocult
- CBC, CMP, CRP, TSH/T4, t-TG Ab IgA neg.
- Colonoscopy normal with random colon and t.ileal bx negative; EGD with duodenal bx (-)
- MR-enterography of small intestine neg.

Case #2: Ella (cont'd)

- Order more testing or treat with confidence?
- First therapy choices?
- Dietary modification?
- Follow-up?

Searching for IBS-D: Differential Diagnoses



IBS-D: Non-Pharmacologic Therapies

Gastroenterol 2006;130: 1377

- Dietary modification
 - Avoid potential triggers: caffeine, alcohol, sorbitol, high fiber foods, high fructose corn syrup, lactose, excess gluten
 - High fiber foods may help some but tailor to individual patient

IBS: Role of FODMAPS

- Fermentable **O**ligosaccharides, **D**isaccharides, **M**onosaccharides and **P**olyols
- Rapidly fermentable short chain carbohydrates
- Associated with abdominal pain, bloating/gas and altered bowel habits
- Fermentation and osmotic effects
- Gibson PR et al, J Gastro Hepatolo 2010;25(2): 252-8

FODMAPS

Avoid

- Fructose: apples, pears, peaches, mangoes
- Lactose: cow, goat, sheep milk, ice cream
- Polyols: asparagus, broccoli, b.sprouts, onions
- Fructans/galactans: cherries, plums, avacodo

Substitute

- Bananas, blueberry, kiwi, citrus
- Lactose-free milk, rice milk, sorbet, gelati
- Carrot, celery, corn, green beans, tomato
- Honeydew melon, citrus, raspberries

IBS: Non-Pharmacological Therapies: Probiotics

- Bifidobacteria infantis
- Lactobacillus GG
- L. acidophilus (alone or in combination)

- All with mixed results of reducing global symptom scores, diarrhea, or pain.

IBS-D Therapy: Loperamide

- Opioid mu receptor agonist
- Slows intestinal transit
- Decreases intestinal secretion
- Quickly absorbed with mostly peripheral activity

In: Sharkey KA, Wallace JL, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12nd ed. New York: McGraw-Hill; 2011.

IBS-D Therapy: Alosetron

- Oral selective serotonin 5-HT₃ antagonist
- Approved for women with diarrhea-predominant IBS
- Restricted FDA use since 2002
- Small number of ischemic colitis cases n=8; severe constipation n=113, in 2000

In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds.
Pharmacotherapy: A Pathophysiologic Approach. 8th ed. New York: McGraw-Hill; 2011.

IBS-D Therapy: Rifaximin

- Gut-selective, non-absorbable antibiotic; broad activity against Gram (+) and (-) anaerobes
- Decreased symptoms of diarrhea and bloating in short term clinical trials
- FDA approved dosing regimen: 550 mg po tid x 14 d; can be repeated x 2

Pimental M, et al. Ann Intern Med 2006; 145: 557-63

Eluxadoline

- Mu- and Kappa- receptor agonists, Delta receptor antagonist
- 100 mg po bid ac; (C IV) controlled substance
- Contraindicated in patients w/o gallbladder
- Sphincter of Oddi spasm/pancreatitis reported in trials

- Curr Gastroenterol Rep 2019;21(6): 25.

Overview of IBS-D Therapies: Mechanisms of Action



*Not FDA-approved for management of IBS-D.

Long-term Surveillance Strategies Based on Age, change in symptoms

- Diseases mis-diagnosed as IBS:
 - Colon cancer in pts > 50 yrs
 - Ovarian cancer in women > 40yrs
 - Inflammatory Bowel Disease
 - Celiac Disease

Take Home Points

- IBS is a chronic disorder characterized by **abdominal pain** with a change in bowel habit frequency and/or consistency
- Therapy is guided by frequency and severity of symptoms
- Differential diagnoses of IBD and celiac disease should be ruled out by history/evaluation
- Re-evaluate patients with a change in their symptoms

References

- Lacey BE et al. Bowel disorders. *Gastroenterol* 2016; 150: 1393-1407.
- Ford AC, et al. Irritable bowel syndrome. *N Engl J Med* 2017; 376(26): 2566-78.
- Munjal A, et al. Update on pharmacotherapy for Irritable Bowel Syndrome. *Curr Gastroenterol Rev* 2019;21(6): 25.
– <https://doi.org/10.1007/s11894-019-0692-7>