IBS: Evidence-Based Approach to Diagnosis & Treatment

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Disclosures

• No speaker’s bureaus
• Scientific advisory boards: Salix, Ironwood
• Research support:
  - Diabetic gastroparesis – Allergan
  - Idiopathic gastroparesis – Takeda
  - IBS-M – Urovant
  - GERD – Impleo
  - Diabetic gastroparesis – Salix
  - Functional dyspepsia – Mayo DDRP
Objectives

• Understand the Rome IV criteria for the diagnosis of IBS
• Appreciate data supporting the use of dietary interventions for the treatment of IBS
• Recognize FDA approved medications for the treatment of IBS
The diagnosis of IBS can be tricky: no mathematical formula can make the diagnosis

\[ \sum \frac{\int \text{Abdominal pain}^3}{\text{Depression}^3 + \text{Anxiety}^2} + \Delta \sqrt{\text{Constipation/Diarrhea}} \]  
\[ \times \text{Bloating} \]

\[ r + \text{Anemia} + \text{Nocturnal symptoms} \times \left[ \begin{array}{c} \text{Extraintestinal symptoms} \\ + \text{Intestinal non-IBS symptoms} \end{array} \right]^{-3} \]
In clinical practice IBS can be a difficult diagnosis to make because…

• Symptoms fluctuate over time
• Symptoms don’t always respond to appropriate therapy
• Other disorders can mimic IBS
• A precise biomarker does not exist
• Guidelines/criteria are not always employed
The Positive Diagnosis of IBS: 5 Key Features

- Clinical history – symptoms are still the key
  - Allergies/ADR, medical, surgical, dietary, psychological
  - Alarm/warning signs
- Physical examination – include DRE
- Rome IV criteria
- Minimal (limited) laboratory tests
- When clinically indicated, colonoscopy or other appropriate tests

Ford, Lacy, Talley, NEJM 2017; 376: 2566-2578
Making the Diagnosis: Supporting Symptoms and Comorbid Conditions

• Supporting symptoms
  • Bloating

• Co-morbid conditions
  • GERD
  • Globus
  • Non-cardiac chest pain
  • Dyspepsia
  • Migraine headaches
  • TMJ syndrome
  • Fibromyalgia
  • Interstitial cystitis
  • Dyspareunia
  • Chronic back pain
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 mixed bowel habits (D and C)

Lacy BE, Mearin FC, et al. Gastroenterology 2016; 150: 1393-1407
Does your patient’s chart look like this?

- **Allergies:** sulfa (cough), penicillin (“achy”), ciprofloxacin (fatigue), metronidazole (“funny taste”), amoxicillin (“spots in my eyes”), aspirin (“blotches”), prednisone (“can’t remember”), diphenhydramine (“fatigue”), desipramine (constipation), PEG-3350 (diarrhea), dicyclomine (“funny taste”), hyoscyamine (“cramps”), linaclotide (diarrhea), lubiprostone (diarrhea), rifaximin (“gas”)
A Dietary History is Critical

- Lactose
- Fructose (juice, soda, sports drinks)
- Fiber (too much or too little?)
- Caffeine
- Gluten
- FODMAPs
- Alcohol (sugar content; complex carbs)
- Supplements/vitamins/minerals
- Weight loss products
Alarm Features for Organic Disorders

- Unintended weight loss (>10% in 3 months)
- Blood in stools not caused (confirmed) by hemorrhoids or anal fissures
- Symptoms that awaken patient
- Fever
- Anemia
- Palpable mass, ascites, lymphadenopathy
- Family history of CRC, Polyposis syndromes, IBD, or celiac disease

If alarm features are present, investigate and treat appropriately

CRC, colorectal cancer; IBD, inflammatory bowel disease
Pearl #1: Conditions that mimic IBS

- Lactose intolerance
- Fructose intolerance
- Small intestine bacterial overgrowth (SIBO)
- Celiac disease
- Non-celiac gluten sensitivity
- IBD
- Microscopic colitis
- Functional diarrhea
- Functional constipation
The value of a physical examination

- Organic disorders can masquerade as IBS
- New diseases/disorders develop over time
- A PE validates the patient’s reporting
- “Laying on of hands” reassures the patient
- Don’t forget Carnett’s test
- Watch for the “closed eyes” sign
- Pelvic floor dyssynergia can be identified
Carnett’s Sign

Figure 2. The Carnett’s sign.

Step 1: The clinician identifies and palpates the point of maximal abdominal tenderness (resting supine position).

Step 2: The patient raises both legs off the examination table (tense position) while the clinician palpates the abdomen. Alternatively, the patient can raise their head and shoulders off the bed, tensing the abdominal wall.

Positive Carnett’s sign: Palpation of abdominal muscles in the tense position elicits the same or more tenderness as the rest position→musculoskeletal source (abdominal wall pain).
Digital Rectal Exam

Position 1
Check anal tone at rest
Ask patient to squeeze

- Puborectalis
- Symphysis pubis
- Internal anal sphincter
- External anal sphincter
Digital Rectal Exam (continued)

Position 2
Insert finger deeper and feel puborectalis muscle
Ask patient to squeeze

Puborectalis
Symphysis pubis
External anal sphincter
Internal anal sphincter
Digital Rectal Exam (continued)

- Angle widens
- Puborectalis relaxes
- Anal canal relaxes
- Perineum descends

Expulsion
Pearl #2: Pelvic Floor Dyssynergia frequently overlaps with IBS-C (and CC)

- PFD is more common in women
- Dyssynergia can usually be identified with a careful rectal examination
- A balloon expulsion test can easily be performed in the office
- HRAM may be required in some patients
- Treatment: physical therapy/biofeedback
Balloon Expulsion Test

1. Patient sits on toilet
2. Patient tries to expel balloon
3. Normal < 60 seconds

Balloon filled with 50 cc water
Anal canal closed
Polyethylene catheter

3-way stopcock

Rome IV Criteria for IBS

Recurrent abdominal pain at least 1 day/week (on average) in the last 3 months associated with ≥ 2 of the following:

- Related to defecation
- Associated with a change in frequency of stool
- Associated with a change in form of stool

Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Rome IV: Limited Diagnostic Tests helps make a positive diagnosis

- In the appropriate patient, consider:
  - “The 4 C’s” - CBC, CRP, fecal calprotectin
  - Celiac serologies
- All patients do **not** require testing
- **No** role for colonoscopy in all patients
- **No** good biomarker yet

**Take Home Message**: Make a positive diagnosis based on symptoms & limited testing and initiate treatment – ideally at the first visit
Management of IBS: Patient Centered Care (What do your patients really want from you?)

- They want you to listen
- Education
- Reassurance
- A positive diagnosis
- Symptom improvement
  - Treatment options explained
Available Treatments for IBS Based on Predominant Symptom

**Bloating/distension**
- Diet (eg, FODMAP)
- Probiotics
- Rifaximin
- GC-C agonists

**Abdominal pain/discomfort**
- Antispasmodics
  - SNRI/TCA
  - Rifaximin (IBS-D)
  - Eluxadoline (IBS-D)
  - Alosetron (IBS-D)
- Lubiprostone (IBS-C)
- Linaclotide (IBS-C)
- Plecanatide (IBS-C)

**Altered bowel function**
- Diarrhea
  - Diet
  - Antispasmodics
  - Loperamide
  - TCA
  - Rifaximin
  - Eluxadoline
  - Alosetron

- Constipation
  - Fiber
  - Osmotic laxatives (PEG)
  - Lubiprostone
  - Linaclotide
  - Plecanatide
  - Biofeedback (dyssynergia)

PEG, polyethylene glycol; SNRI, serotonin and norepinephrine reuptake inhibitor
Talley, Lacy, Ford. NEJM 2017
Treatment Depends on Severity of IBS

- Psychological treatments
- Goal: improved function
- Continuing care
- Follow-up visit
- Manage stress
- Drug therapy
- Diet, lifestyle advice
- Positive diagnosis
- Explain, reassure

Therapies with Limited Utility in IBS

<table>
<thead>
<tr>
<th>Therapy (subtype)</th>
<th>Quality of Evidence</th>
<th>ACG Task Force Conclusions¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loperamide (IBS-D)</td>
<td>Very low</td>
<td>Insufficient evidence to recommend use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improves diarrhea, not abdominal pain</td>
</tr>
<tr>
<td>PEG (IBS-C)</td>
<td>Low</td>
<td>Insufficient evidence to recommend use²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improves SBMs, not abdominal pain</td>
</tr>
<tr>
<td>Prebiotics &amp; Synbiotics (all subtypes)</td>
<td>Very low</td>
<td>1 study with prebiotics; 2 studies of synbiotics; unclear risk of bias; small sample size</td>
</tr>
<tr>
<td>Probiotics (all subtypes)</td>
<td>Low</td>
<td>Insufficient/conflicting data on specific species, strains, preparations</td>
</tr>
<tr>
<td>Antispasmodics (all subtypes)</td>
<td>Very low</td>
<td>May relieve postprandial pain; unlikely to be effective for chronic pain; AEs may limit use</td>
</tr>
</tbody>
</table>

¹ACG, American College of Gastroenterology; AEs, adverse events; SBMs, spontaneous bowel movements

Dietary Therapy for IBS

- Elimination diet
- IgG elimination diet
- Low carbohydrate
- Low fructose/fructan
- Lactose free diet
- Paleo diet
- Low gluten
- Low FODMAP
Dietary Recommendations for IBS

How often do gastroenterologists recommend different dietary therapies for patients?

Responders, %

- High fiber
- Lactose-free
- Gluten-free
- Low fat
- Low FODMAP

A Low-Gluten Diet for IBS

- 2 RCTs
- 1 trial – low risk of bias; 1 trial – risk unclear
- N= 111
- GFD was associated with reduced global IBS symptoms (RR 0.42, 95% CI 0.11 to 1.55; NS)
- Take home message: little data to support a commonly employed treatment

Gluten-free diets can be difficult

“I’ve only been gluten-free for a week, but I’m already really annoying.”
A low FODMAP Diet

**Fermentable Oligo-, Di-, Monosaccharides And Polyols**

- **Excess Fructose**: Honey, apples, pears, peaches, mangos, fruit juice, dried fruit
- **Fructans**: Wheat (large amounts), rye (large amounts), onions, leeks, zucchini
- **Sorbitol**: Apricots, peaches, artificial sweeteners, artificially sweetened gums
- **Raffinose**: Lentils, cabbage, Brussels sprouts, asparagus, green beans, legumes

FODMAPs & the GI Tract

Normal: hydrolysis and absorption of fructose, lactose, and GOS. Abnormal: partial/insufficient digestion and absorption of FODMAPs.

- Polyols
- Fructans
- Fructose
- Galactose
- Glucose
- Lactose
- GOS

↑osmotic load

↑speed of small intestine transit
↑content of water in biomass

GI symptoms: bloating, ab pain, diarrhea, altered bowel movements, gas

Cognitive and emotional factors

Changes in microbiome:
↓Luminal pH

Bacterial fermentation:
↑Gas production (H₂, CH₄, CO₂)

SCFAs: Butyrate, Acetate, Propionate

Effects on gut:
- Motility
- Pemeability
- Immune activation
- Visceral sensation

Proposed additional mechanisms:
- ↑Mucosal release serotonin
- ↑Mast cell activation

Visceral hypersensitivity

Small Bowel
Colon
A Low FODMAP Diet vs. Modified NICE Guidelines in US Adults with IBS-D

- Single-center, RCT; Rome III criteria
- Low FODMAP vs. mNICE x 4 weeks; 2 wk screening
- Primary endpoint: % reporting adequate relief of IBS-D symptoms ≥50% of weeks 3-4
- 92 Pts; 65 women; median age = 42.6
- 52% of low FODMAP vs. 41% of mNICE met primary endpoint (p = 0.31)
- Low FODMAP more likely to provide relief of abdominal pain (51% vs. 23%; p = .008) and bloating (p = .002)

Low FODMAP Diets: It’s not so easy

- Resources differ on low FODMAP diets
- What is the cut-off for FODMAP content?
- Total meal FODMAPs should be counted, not individual FODMAPs
- Many patients can’t stick to the diet
- Often requires significant time counseling
- How should foods be reintroduced?
- Nutritional issues with long-term use
Low FODMAP vs. Traditional Dietary Advice

• Multicenter, parallel study – Rome III patients
• 33 – Low FODMAP; 34 – traditional IBS diet
• 4 week study; symptoms assess using IBS-SSS

Bohn et al, Gastroenterology 2015; 149: 1399-1407
Micronutrient Deficiencies with low FODMAP diet

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low FODMAP (n = 41)</th>
<th>mNICE (n = 37)</th>
<th>P value within group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 4</td>
<td>Baseline</td>
</tr>
<tr>
<td>Energy (kcals)</td>
<td>2043 ± 653</td>
<td>1691 ± 600.7</td>
<td>2005 ± 511</td>
</tr>
<tr>
<td># Daily Meals</td>
<td>5.43 ± 1.7</td>
<td>4.92 ± 1.5</td>
<td>5.52 ± 1.7</td>
</tr>
<tr>
<td>Polyunsaturated Fatty Acids (g)</td>
<td>18.6 ± 7.2</td>
<td>17.6 ± 9.8</td>
<td>20.1 ± 7.9</td>
</tr>
<tr>
<td>Retinol (mcg)</td>
<td>493.9 ± 379.2</td>
<td>350.2 ± 179.0</td>
<td>427.9 ± 207.5</td>
</tr>
<tr>
<td>Thiamin (Vitamin B1) (mg)</td>
<td>1.6 ± 0.6</td>
<td>1.3 ± 0.6</td>
<td>1.8 ± 0.6</td>
</tr>
<tr>
<td>Riboflavin (Vitamin B2) (mg)</td>
<td>2.0 ± 0.8</td>
<td>1.7 ± 0.6</td>
<td>1.9 ± 0.6</td>
</tr>
<tr>
<td>Vitamin B6 (mg)</td>
<td>1.7 ± 0.6</td>
<td>2.1 ± 0.8</td>
<td>1.8 ± 0.8</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>969.5 ± 422.9</td>
<td>752.3 ± 300.3</td>
<td>961.4 ± 375.8</td>
</tr>
</tbody>
</table>

No significant differences from baseline were seen for daily intake of cholesterol, saturated fatty acids, monounsaturated fatty acids, caffeine, beta carotene, Total Alpha-Tocopherol Equivalents, vitamin D, vitamin E, vitamin K, vitamin C, niacin, pantothenic acid, folate, & vitamin B12.

Probiotics: Putative Mechanisms of Action

• Competitive inhibition
• Barrier protection
• Immune effects
• Anti-inflammatory effects
• Production of various substances (enzymes, SCFA, bacteriocidal agents)
• Ability to alter local pH and physiology
• Provides nutrition to colonocytes

Forest plot of randomized controlled trials of probiotics vs placebo in IBS: effect on global symptom or abdominal pain scores

Ford, Harris, Lacy, Quigley, Moayyedi. APT 2018; 48:1044-1060.
Medical Treatments for IBS-C

- Probiotics
- - little data to support their use
- Fiber
- Osmotic agents
- Chloride channel activators
- Guanylate cyclase C activators
- CAM
PEG 3350+E Improves SBMs in IBS-C but not Pain

Mean at Week 4

* P < 0.0001

# SBMs

- Placebo (n=71)
- PEG 3350+E (n=68)

Pain Level

SBMs = spontaneous bowel movements; PEG = polyethylene glycol
PEG 3350+E is not approved for use in the US

Efficacy of Linaclotide in Patients With IBS-C

ANCOVA = analysis of covariance; RW = randomized withdrawal

*P < 0.0001 for linaclotide patients vs placebo patients (ANCOVA).
†P < 0.001 for linaclotide/linaclotide patients vs linaclotide/placebo patients (ANCOVA).

Linaclotide Phase 3 IBS-C Trial: Abdominal Pain Over 26 Weeks

ITT population, observed cases, LS-mean presented: \( P \)-values based on ANCOVA at each week. Bars represent 95% CI.

\( P=0.0007 \) for week 1
\( P<0.0001 \) for weeks 2-26

N=804


ITT, intention to treat; LS, least squares.
Plecanatide

- 16 aa peptide analog of uroguanylin
- Activates guanylate cyclase C receptors (GC-C) with increase in intestinal fluid secretion
- FDA approved:
  - CIC (2017)
  - IBS-C – 1-24-18

Miner et al. Am J Gastroenterol 2017; 112: 613-621.
Plecanatide for IBS-C: Rome III Patients

Responders defined as a patient who was both an Abdominal Pain responder (≥ 30% reduction in worst abdominal pain) and Stool Frequency Responder (an increase of ≥ 1 CSBM from baseline), in the same week, for ≥ 6 weeks of the 12 treatment weeks.

Brenner et al, Am J Gastroenterol 2018; 113:735-745
Medical Treatments for IBS-D

- Diet
- Probiotics
- Anti-diarrheal agents
- Smooth muscle anti-spasmodics
- Bile acid sequestrants
- 5-HT₃ antagonists
- Antidepressants
- Antibiotics
- Mu-opioid agonists/delta-opioid antagonists
- Psychological interventions
- CAM

CAM, complementary and alternative medicine. Talley, Lacy, Ford. NEJM 2017
Ondansetron for IBS-D

Effect of Ondansetron 4-8 mg TID for 5 Weeks in Patients with Rome III IBS-D (N=120)*

- *Randomized, double-blind, dose-titration study. Primary endpoint was average stool consistency in last 2 weeks of treatment.
- Improvements in urgency, frequency, bloating but NOT pain.
Forest plot of randomized controlled trials of antidepressants versus placebo in terms of effect on abdominal pain in IBS

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antidepressants</th>
<th>Placebo</th>
<th>Risk ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td>M–H, Random, 95% CI</td>
</tr>
<tr>
<td>1.2.1 Tricyclic antidepressants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heefner (1978)</td>
<td>10</td>
<td>22</td>
<td>12</td>
<td>22 13.5%</td>
</tr>
<tr>
<td>Vij (1991)</td>
<td>15</td>
<td>25</td>
<td>22</td>
<td>25 18.0%</td>
</tr>
<tr>
<td>Vahedi (2008)</td>
<td>2</td>
<td>14</td>
<td>7</td>
<td>14 5.0%</td>
</tr>
<tr>
<td>Ghadir (2011)</td>
<td>14</td>
<td>38</td>
<td>20</td>
<td>24 16.1%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>99</td>
<td>85</td>
<td>52.5%</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>41</td>
<td>61</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.04; Chi² = 4.64, df = 3 (P = 0.20); I² = 35%
Test for overall effect: Z = 3.02 (P = 0.002)

1.2.2 Selective serotonin re-uptake inhibitors

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antidepressants</th>
<th>Placebo</th>
<th>Risk ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuiken (2003)</td>
<td>10</td>
<td>17</td>
<td>16</td>
<td>16 17.1%</td>
</tr>
<tr>
<td>Tabas (2004)</td>
<td>30</td>
<td>44</td>
<td>27</td>
<td>46 18.6%</td>
</tr>
<tr>
<td>Vahedi (2005)</td>
<td>6</td>
<td>22</td>
<td>19</td>
<td>22 11.7%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>83</td>
<td>84</td>
<td>47.5%</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>46</td>
<td>62</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.31; Chi² = 14.38, df = 2 (P = 0.0008); I² = 86%
Test for overall effect: Z = 1.28 (P = 0.20)

Total (95% CI) 182 169 100.0% 0.62 [0.43, 0.88]
Total events 87 123

Heterogeneity: Tau² = 0.15; Chi² = 21.75, df = 6 (P = 0.001); I² = 72%
Test for overall effect: Z = 2.68 (P = 0.007)
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.85), I² = 0%

Favors antidepressants Favors placebo

Ford, Lacy, Harris, Quigley, Moayyedi. Am J Gastroenterol 2018; epub ahead of print.
Rifaximin Trials: Global Relief of IBS Without Constipation

- 2 Phase 3 randomized controlled trials; N=1260 patients
- Rifaximin 550 mg TID x 2 weeks; patients followed additional 10 weeks
- 40.7% vs. 31.7% with adequate relief of global symptoms ($P<0.001$)

T-I, TARGET 1 trial; T-II, TARGET 2 trial; Comb, Combination of both trials. *Rifaximin is FDA-approved for non-constipation IBS.

Retreatment with Rifaximin Study Design - Target 3

Screening/Treatment 1 Phase
Study Day 1

7-13 d
PBO

2w RFX
4w f/u

Treatment 2 Phase

2w f/u

Up to 18w

Maintenance Phase 1

Non-Responders Withdrawn

Responders with recurrent symptoms

Treatment 3 Phase/DBR Treatment Phase

Primary Evaluation Period

1:1

2w RFX
4w f/u

6w

2w RFX
4w f/u

Maintenance Phase 2

Follow up

2w PBO
4w f/u

6w

2w PBO
4w f/u

Up to 18w

Primary Evaluation Period

1:1

2w RFX
4w f/u

6w

2w RFX
4w f/u

Follow up

4w EOS

Obtain Daily/Weekly Symptom Diary

* Stool sample collection

Lembo et al Gastroenterol 2017
Retreatment with Rifaximin in IBS-D
IBS-related Abdominal Pain and Stool Consistency (Worst Case Analysis)

First and Second Repeat Treatment Phases

Responder: Patient responding to IBS-related Abdominal Pain (≥30% improvement) and Stool consistency (≥50% decrease in # BMs with type 6 or 7) from baseline for ≥ 2 of the 4 weeks


N = 1074
Eluxadoline for IBS-D: Rationale

- Mixed mu (μ) opioid receptor agonist / delta (δ) opioid receptor antagonist
- Low systemic absorption and bioavailability
  - Low potential for drug–drug interactions
- Animal studies suggest eluxadoline should improve the diarrheal symptoms of IBS-D with limited constipation and durable analgesia

## Definition of primary endpoint: composite responder

<table>
<thead>
<tr>
<th>FDA guidance / EMA draft guidance</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Responder must meet both criteria on same day:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Daily pain responder:</strong></td>
<td><strong>AND</strong></td>
</tr>
<tr>
<td>WAP scores improved by $\geq 30%$ compared to average baseline pain</td>
<td></td>
</tr>
</tbody>
</table>

- Above met on at least 50% of days in Weeks 1–12 (FDA), Weeks 1–26 (EMA)
- Minimum 60 days (FDA) / 110 days (EMA) diary compliance
- Bonferroni adjustment: to preserve the family-wise error rate for each active group vs placebo ($p<0.025$)

BM, bowel movement
Primary endpoint: composite responders – pooled data

Responders (%)

Weeks 1–12

Weeks 1–26

N=808
N=809
N=809

N=808
N=806
N=809

Δ 10.3*
Δ 7.2*
Δ 11.5*
Δ 9.5*

PBO
75 mg ELX
100 mg ELX


*p<0.001
Safety of Eluxadoline in Patients with IBS with Diarrhea

- 2,814 IBS-D patients (Rome III criteria)
- Placebo vs. eluxadoline (75 or 100 mg b.i.d.)
- 1 Phase 2 study (12 weeks) and 2 Phase 3 studies (26 and 52 weeks)
- Most frequent AEs:
  - Constipation (2.5% vs. 7.4% vs. 8.1%)
  - Nausea (5.0 vs. 8.1 vs. 7.1%)
- 10 Patients had Sphincter of Oddi Spasm (0.5%); all occurred in patients with prior CCY

Alternative Therapies for IBS

- STW5 (Iberogast) and STW5-II
- Padma Lax – Tibetan formula of 12 herbs - for IBS-C
- Peppermint oil – meta-analysis positive
- IBgard – 4 wk. positive trial
- CBT – better than education; wait-list
- Yoga – 6 RCTs; data unclear
- Acupuncture – not better than placebo
- Hypnotherapy – better than antispasmodics; equal to a low FODMAP diet

Talley, Lacy, Ford. NEJM 2017
Gut directed hypnotherapy is similar to low FODMAP diet for IBS

- RCT; 3 arms; n = 74
- Hypnotherapy vs. low FODMAP vs. combination
- 6 week trial
- Median age ~ 38 yrs
- Results: improvement occurred in all 3 groups
  - No difference between the 3 groups

Peters et al, APT 2016; 44: 447-459
What’s coming down the pike?

- Probiotic trials
- New diet trials
- IBS-M study (vibergon; β3-adrenergic receptor agonist)
- IBS-C (tenapanor; Na-H exchanger)
- IBS-D study (ORP-101; partial mu agonist; full kappa antagonist)
- Agomelatine – a melatonin analog
- Further trials on glutamine?
Summary

• IBS is a constantly evolving field
• Our understanding of IBS physiology continues to expand
• Multiple treatment options are now available for both IBS-C and IBS-D
• Expect new treatment options within the next few years
• Expect more information on diet, probiotics and alternative therapies
Questions?