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IBS: Updates on Diagnostics and Therapeutics for the Primary Practitioner

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Rome IV: Diagnostic Criteria*

- Recurrent abdominal pain [or discomfort-deleted] on average at least 1 day per week in the last 3 months associated with 2 or more of the following:

Pain related to defecation **&/OR** [deleted] Associated with change in stool form **&/OR** [deleted] Associated with change in stool frequency

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

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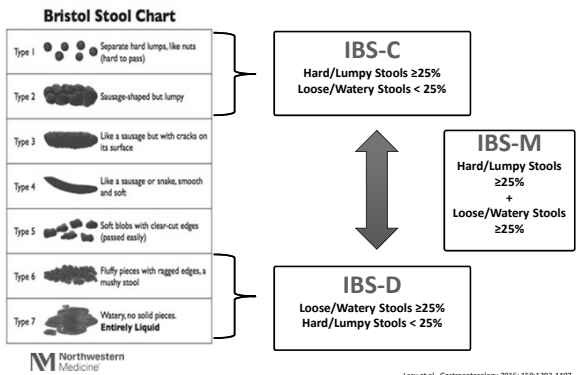
Lacy et al., Gastroenterology 2016; 150:1393-1407.

Rome IV IBS Subtypes



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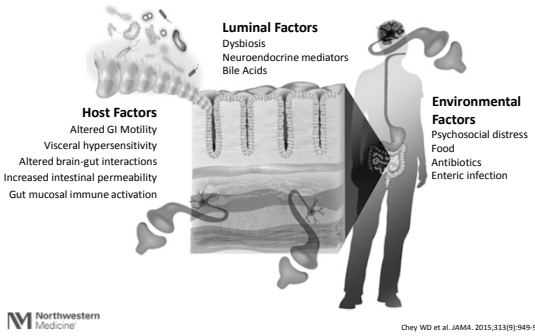
Lacy et al., Gastroenterology 2016; 150:1393-1407.

Overview of IBS Pathophysiology



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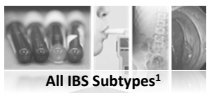
Chey WD et al. *JAMA*. 2015;313(9):949-958.

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



All IBS Subtypes[1]

CBC

Age-appropriate CRC screening

IBS-D[1,2]	IBS-M[1]	IBS-C[1]
• CRP or fecal calprotectin • IgA TtG ± quantitative IgA • When colonoscopy performed, obtain random biopsies • SeHCAT, fecal bile acids, or serum C_4 where available • Anti-CdtB/anti-vinculin antibodies[2]	• CRP or fecal calprotectin • IgA TtG ± quantitative IgA • Stool diary • Consider abdominal plain film to assess for fecal loading	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.
CBC, complete blood count; CRC, colorectal screening; CRP, C-reactive protein
; SeHCAT, selenium homocholic acid taurine; Ttg, tissue transglutaninase.

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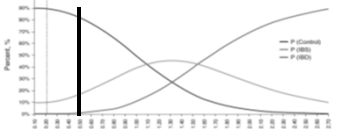
1. Chey WD et al. *JAMA*. 2015;313(9):949-958; 2. Pimentel M et al. *PLoS ONE*. 2015;10(5):e0126438

Fecal calprotectin and CRP may essentially rule-out IBD in patients with IBS symptoms

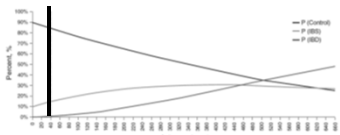
Systematic Review: 12 studies; N=2145:1059 IBD, 595 IBS, 491 controls

Human adult studies: Pts with confirmed IBD compared ESR, CRP, Fecal Calprotectin, Fecal Lactoferrin with IBS or controls

Naïve Bayes statistics to assess probability of having IBS or IBD based on biomarker values



CRP	Percent likelihood HC	Percent likelihood IBS	Percent likelihood IBD
0.1	89.9	9.8	0.2
0.2	89.8	9.9	0.3
0.3	88.4	11.2	0.4
0.4	85.8	13.6	0.6
0.5	82.1	16.8	1.1
0.6	77.4	20.8	1.8
0.7	71.7	25.8	3.0
0.8	65.1	30.2	4.7
0.9	57.9	35.0	7.2
1.0	50.2	39.3	10.6



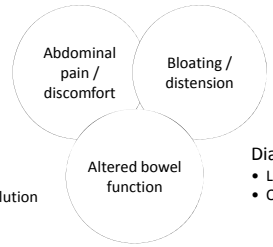
Calprotectin	Percent likelihood HC	Percent likelihood IBS	Percent likelihood IBD
10	88.6	11.0	0.4
20	87.1	12.4	0.5
30	85.5	13.7	0.8
40	84.1	14.9	1.0
50	82.7	16.0	1.3
60	81.4	17.0	1.6
70	80.1	18.0	1.9
80	78.8	18.9	2.3
90	77.6	19.7	2.7
100	76.3	20.6	3.1

Menees SB et al. AJG 2015;110:444-454.

Treatment of IBS (Then)

Abdominal pain / discomfort
Antispasmodics
Antidepressants

Bloating
•5-HT_4 agonist
•Dietary changes



Constipation
- Fiber
- MOM /PEG solution

Diarrhea
- Loperamide
- Other opioids

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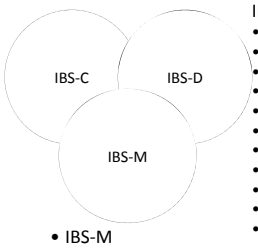
Treatment of IBS (Now)

IBS-C
- Linaclotide*
- Lubiprostone*
- CBT/Hypnotherapy
- Diet Modification
- SSRIs
- Probiotics
- Elobixibat



IBS-D
•CBT/Hypnotherapy
•Diet Modification
•Rifaximin*
•TCAs
•Enterra-GAM*
•Eluxadoline*
•Alosetron*
•Probiotics
•Ibgard
•Bile-acid binding agents
•Anti-spasmodics

- IBS-M
  CBT/Hypnotherapy
  Diet Modification
  Probiotics
  IBgard

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* denotes FDA approval

AGAI/ACG Technical Review of IBS Pharmaceuticals

Therapeutic	AGA Recommendation (Compared to No Drug Treatment)	AGA Quality of Evidence	ACG Recommendation	ACG Quality of Evidence
Linaclotide	Strong IBS-C	High	Strong IBS-C	High
Lubiprostone	Conditional IBS-C	Moderate Quality	Strong IBS-C	Moderate
PEG Laxatives	Conditional IBS-C	Low Quality	Weak IBS-C	Very Low
Rifaximin	Conditional IBS-D	Moderate Quality	Weak IBS-D	Moderate
Alosetron	Conditional IBS-D	Moderate Quality	Weak Females IBS-D	Moderate
Loperamide	Conditional IBS-D	Low Quality	Strong against	Very Low
Tricyclics	Conditional IBS	Low Quality	Weak	High
SSRIs	Conditional AGAINST USE	Low Quality		
Antispasmodics	Conditional IBS	Low Quality	Weak	Low

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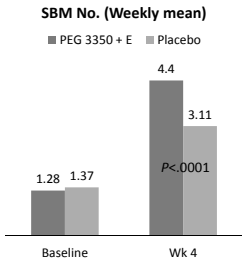
Weinberg et al. Gastroenterology 2014;147:1146-48.
Chang L et al. Gastroenterology 2014;147:1149-72.
Ford et al. Am J Gastroenterol 2014;109:S2-26.

PEG 3350 + Electrolytes for IBS-C

- RCT of PEG 3350 + E (n=68) vs placebo (n=71)
- Primary endpoint
  - No. SBMs/week in Wk 4
- PEG 3350 + E significantly improved no. SBMs/d, stool consistency, and straining vs placebo (*P*<.0001)
  - PEG 3350 + E significantly improved abdominal pain from baseline (*P*<.005)
  - *Not* observed with placebo



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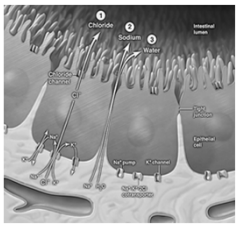
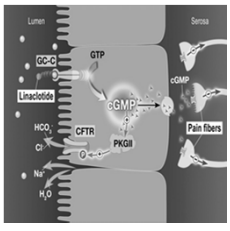
Chapman RW et al. *Am J Gastroenterol*. 2013;108:1508-1515.

Mechanism of Lubiprostone and Linaclotide in IBS-C

Lubiprostone:
ClC-2 Chloride Channels Regulate Fluid Secretion[1]

Linaclotide:
Guanylate Cyclase-C Activation[2]





Both: Increased luminal fluid secretion & intestinal transit

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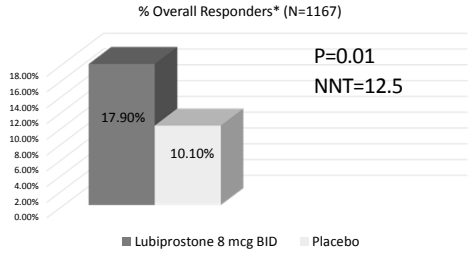
1. Camilleri M. *Aliment Pharmacol Ther*. 2010:31:35-46.
2. Andresen V, et al. *Drugs of the Future*. 2008;33:570-576.

Lubiprostone: IBS with Constipation



*Defined as monthly responder for ≥2 of 3 months. Monthly responder defined as having at least moderate relief for 4 of 4 weeks or significant relief for 2 of 4 weeks.

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Drossman DA et al. *Aliment Pharmacol Ther*. 2009;29:329-341.

Lubiprostone in the Clinic

Dosage for IBS-C
8 µg BID but can be increased to 24 µg BID

Take with food and water to minimize nausea

- Contraindicated mechanical GI obstruction

Most Common Adverse Events in IBS-C Trials*

Adverse Events	Placebo (n=435)	Lubiprostone 8 µg BID (n=1,011)
	%	
Nausea	4	8
Diarrhea	4	7
Abdominal pain	5	5
Abdominal distension	2	3

*Includes only those events associated with treatment (possibly or probably related, as assessed by investigator)

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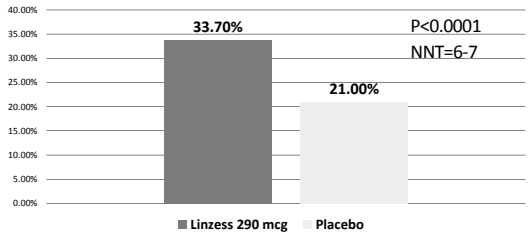
Amitiza (lubiprostone) [prescribing information]. Sucampo Pharma Americas, LLC; Bethesda, MD: April 2013.

IBS-C: Linaclotide

Primary Responders* (N=1604)



*Primary end point defined as ≥30% reduction in abdominal pain plus an increase of ≥1 complete spontaneous bowel movement from baseliine same week 6/12 weeks

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Chey WD et al. *Am J Gastroenterol 2012;107(11):1702-12.*
Rao SSC et al. Am J Gastroenterol 2012;101(11):1714-24.

Linaclotide in the Clinic

Dosage[1]
290 µg once daily.* Take on empty stomach ≥30 minutes prior to first meal of the day.

May be mixed with water or applesauce for administration to patients with difficulty swallowing.

Contraindicated in pediatric patients up to 6 years of age. Avoid use in children 6 through 17 years of age.

Most Common Adverse Events in IBS-C Trials*

	Placebo n=798	Linaclotide 290 mcg n=402
	%	%
Diarrhea	3	20
Abdominal pain†	5	7
Flatulence	2	4
Abdominal distension	1	2
Viral gastroenteritis	1	3
Headache	3	4

*Occurring in ≥2% of linaclotide-treated patients and at an incidence greater than placebo.
†Includes abdominal pain, upper abdominal pain, and lower abdominal pain.

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LINZESS (linaclotide) [prescribing information]. Forest Pharmaceuticals, Inc. St. Louis, MO: July 2014.

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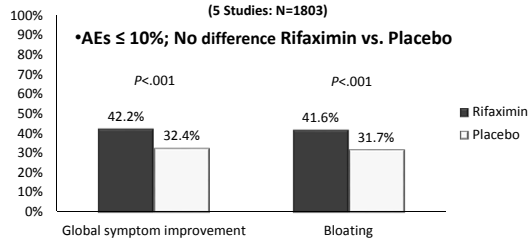
IBS-D

Meta-Analysis: Rifaximin Significantly Relieves Global Symptoms & Bloating

NNT=10

Systematic Review and Meta-analysis of Rifaximin vs Placebo
(5 Studies: N=1803)

•AEs ≤ 10%; No difference Rifaximin vs. Placebo



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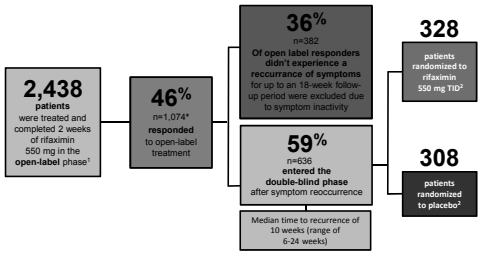
Menees SB et al. *Am J Gastroenterol.* 2012;107(1):28-35.

TARGET 3: Rifaximin Retreatment and Safety Study

*Responder: ≥30% reduction in mean weekly abdominal pain score + ≥50% reduction in # days per week with Bristol 6-7 stools for ≥ 2 of 4 weeks



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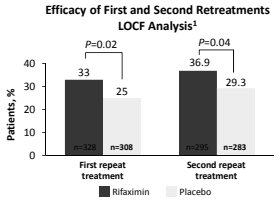
Lembo A et al. AJG 2014:109(10): Abstract

TARGET 3: Efficacy of First and Second Retreatments



LOCF, last observation carried forward.
Responder defined as subjects responding to IBS-related Abdominal Pain and Stool Consistency for ≥2 of 4 weeks.
Recurrence defined as a loss of response for ≥3 of 4 weeks.

Urgency and bloating improved significantly with both repeat treatments

Abdominal pain and stool consistency improved significantly with first retreatment

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1 Lembo A et al. AJG 2014:109(10): Abstract
2 Chey WD et al. DDW 2015: Abstract 313

Rifaximin in the Clinic

Dosage
550 mg TID for 14 days, with up to 2 retreatments with the same regimen[1]

Most Common Reported Adverse Events (≥2%)*[2]

Adverse Events	Rifaximin 550 mg (n=1,008) n (%)	Placebo (n=829) n (%)
Headache	55 (5.5)	51 (6.2)
URT infection	45 (4.5)	47 (5.7)
Nausea	41 (4.1)	31 (3.7)
Abdominal pain	40 (4.0)	39 (4.7)
Diarrhea	35 (3.5)	26 (3.1)
Urinary tract infection	32 (3.2)	18 (2.2)

*Pooled analysis of Phase 2b and 3 trials of rifaximin in non-IBS C

Pooled safety analysis demonstrated no difference between rifaximin and placebo for any adverse event[2]

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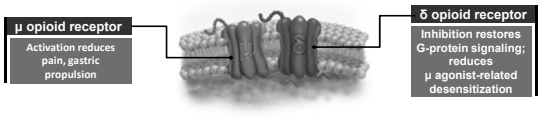
1. XIFAXAN® (rifaximin) [prescribing information]. Salix Pharmaceuticals; Raleigh, NC: May 2015;
2.Schoenfeld P et al. *Aliment Pharmacol Ther*. 2014;39:1161-1168.

Eluxadoline in IBS-D

- Mixed opioid receptor activity
  - Mu (μ) opioid receptor agonist
  - Delta (δ) opioid receptor antagonist and kappa (κ) opioid receptor agonist[1,2]
- Low systemic exposure after oral administration[2]
- Animal studies suggest eluxadoline can improve the diarrheal and hyperalgesia symptoms of IBS-D with limited constipation[1,2]



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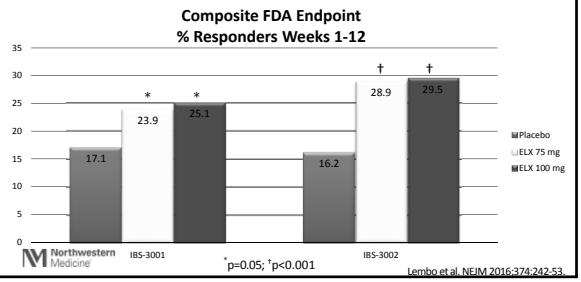
1. Fujita W et al. *Biochemical Pharmacology*. 2014. http://dx.doi.org/10.1016/j.bcp.2014.09.015;
2. Wade PR et al. *British Journal of Pharmacology*. 2012;167:1111-1125;
3. VIBERZI™(eluxadoline) [package insert] Cincinnati, OH: Forest Pharmaceuticals, Inc.; May 2015.

Eluxadoline

2 Phase III trials (IBS-3001; IBS-3002) IBS-D Rome III Criteria
N=2427; Placebo; Eluxadoline 75 mg BID or 100 mg BID x26 weeks (12 wks FDA:26 wks EMA)
1^0 Endpoint Responder: ≥30% reduction in daily WAP compared to ave baseline pain
+ BSS <5 for 50% trial days



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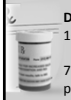
*p=0.05; †p<0.001

Lembo et al. NEJM 2016;374:242-53.

Eluxadoline in the Clinic



Dosage
100 mg BID taken with food

75 mg BID with food in patients who
- do not have a gallbladder
- are unable to tolerate 100 mg BID
- are receiving concomitant OATP1B1 inhibitors
- have mild or moderate hepatic impairment

Contraindications
- Bile duct obstruction
- Sphincter of Oddi disease or dysfunction
- Pancreatitis
- Severe liver impairment (Child-Pugh Class C)
- Severe constipation
- Patients who consume >3 alcoholic drinks per day

Increased risk of pancreatitis (4/1666)
SOD events—pain+ inc LFTs (10/1666)
pts without a GB and (+) ETOH use

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Lembo AJ et al. *N Engl J Med*. 2016;374:242-253.
VIBERZI (eluxadoline) [prescribing information]. Forest Pharmaceuticals, Inc; Cincinnati, OH: May 2015.

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Global IBS Symptoms: Natural and Alternative Therapies

Fiber for IBS: Meta-analysis

- 12 studies, 591 patients
- 2 studies recruited IBS-C only
- 7/12 studies had a Jadad score ≥4

Improvement: Fiber (%)	Improvement: Placebo (%)	RR symptoms remain (95% CI)
48	43	0.87 (0.76-1.00) P=.05

- No significant heterogeneity and no funnel-plot asymmetry
- No significant effect of fiber (RR=0.90; 95% CI = 0.75-1.08) seen when only the 7 good-quality trials were evaluated

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Ford AC et al. *BMJ*. 2008;337:1388-92.

What Are FODMAPs?

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
Lactose	Milk (cow, goat, or sheep), custard, ice cream, yogurt, soft unripened cheeses (eg, cottage cheese, ricotta)
Sorbitol	Apricots, peaches, artificial sweeteners, artificially sweetened gums
Raffinose	Lentils, cabbage, brussels sprouts, asparagus, green beans, legumes

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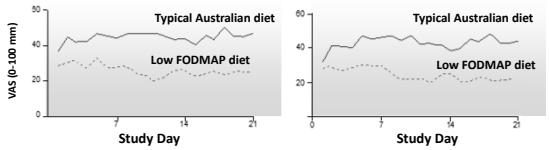
1. Shepherd SJ et al. *Clin Gastroenterol Hepatol*. 2008;6:765-771; 2. Shepherd SJ Gibson PR. *J Am Diet Assoc*. 2006;106:1631-1639; 2. 3. Barrett JS Gibson PR. *Ther Adv Gastroenterol*. 2012;5:261-268.

FODMAP Diet Reduces Functional GI Symptoms

Effects of Diet on Functional GI Symptoms in Controlled, Single-Blinded Crossover Study (N=30)



FODMAP, fermentable oligo-di-monosaccharides and polyols.

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Halmos EP et al. *Gastroenterology*. 2014;146:67-75.

Peppermint Oil (PO)

- Peppermint oil: 1^0 active component L-menthol
  - Anti-spasmodic, inflammatory, 5-HT_3, bacterial properties
  - Approved as 1st-line therapy for IBS by European Medicine Agencies (EMA)
  - Recent Meta-Analysis:
    - Reduces global IBS symptoms and abdominal pain
    - More effective than anti-spasmodics, TCAs, fiber
    - NNT 2-3
    - Associated with increased adverse events (heartburn, abdominal pain, anal burning)
- Potential benefit if side-effects can be minimized/mitigated

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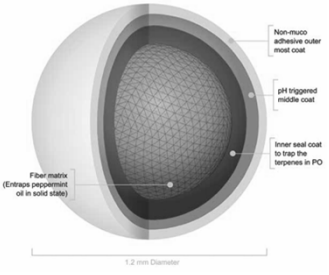
Khanna et al. J Clin Gastroenterol;48(6):505-512; Enck et al. Eur J Gastroenterol Hepatol 2010;22:1402-1411
Ford et al. Am J Gastroenterol 2014;109:52-26

IBS Reduction Evaluation and Safety Trial (IBSREST™)

IBgard®: Medical food specially designed ultra-purified PO microsphere formulation with targeted sustained release into the SI



- 4-week USA RPCT for
- moderate/severe IBS-M/D
  - 180 mg (2 capsules TID)
  - Placebo
- 18-60 y/o Rome III Criteria
  - N=72 (75%F:25%M)
  - 53% IBS-D:47% IBS-M
- Abdominal pain score ≥4 (0-10)
- Total IBS Symptom Score (TISS) ≥2
  - Baseline IBgard Score: 2.93
  - Baseline Placebo Score: 2.76
- 1^0 analysis: Changes in TISS

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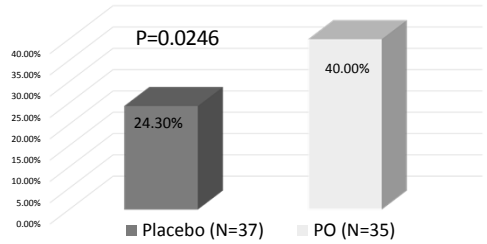
Cash et al. Dig Dis Sci 2015: Accessed online 8/15.

IBSREST™ Trial

Reduction In TISS* at 4 Weeks



* Components of TISS include abd pain/discomfort, bloating/distention, constipation/diarrhea, pain at evacuation, passage gas/mucus, sense IE, urgency

Total adverse events: PO=2 (5.7%) PBO=4 (10.8%)

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Cash et al. Dig Dis Sci 2015: Accessed online 8/15.

Psychological Therapies Improve IBS Symptoms

- Psychosocial therapies have been shown to be effective in improving IBS symptoms
  - Cognitive behavioral therapy (CBT)
  - Hypnotherapy
  - Multi-component psychological therapy
  - Multi-component psychological therapy administered by phone
  - Dynamic psychotherapy
- Use limited by lack of available skilled therapists in managing IBS
- Northwestern GI Behavioral Health Program
  - Drs. Sarah Kinsinger and Quinton

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Ford AC et al. *Am J Gastroenterol*. 2014;109(Suppl 1):S2-S26.

Summary

- **IBS is a common disorder affecting 10-14% of the international population**
- **Pathogenesis heterogeneous**
- **Diagnostics minimized**
  - IBS-D: CRP, Fecal Calprotectin, Celiac serologies, colonoscopy for alarm signs/symptoms + biopsies
  - IBS-C: Colonoscopy for alarm signs/symptoms
- **Treatments based on subtype but no specific algorithms**
  - Prognostic data lacking or poor
  - Decision based on personal biases → Pharmaceutical versus "Natural/CAM"
  - Key to allow patient to participate in the process→Improved outcomes

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