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2020 Third Annual National Conference

November 19-21, 2020

Red Rock Hotel – Las Vegas, NV



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Irritable Bowel Syndrome-Constipation

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Disclosures

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Disclosures

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Steering Committee: Salix, Clinical Area- IBS-D, IBS-S, hepatology

Case Study

- Patient Profile: 48-yr-old woman
- Presenting Symptoms: worsening constipation, bloating, and gas over the past month. She has increased fiber intake in her diet and tried OTC psyllium, which help her bowel movements but worsened bloating and caused some abdominal pain.
- What other information would you like to have? Which tests/labs should be offered?

Red Flags for Constipation

Unexplained
change in bowel
habit

Unexplained weight
loss, iron deficiency
anemia, nocturnal
symptoms

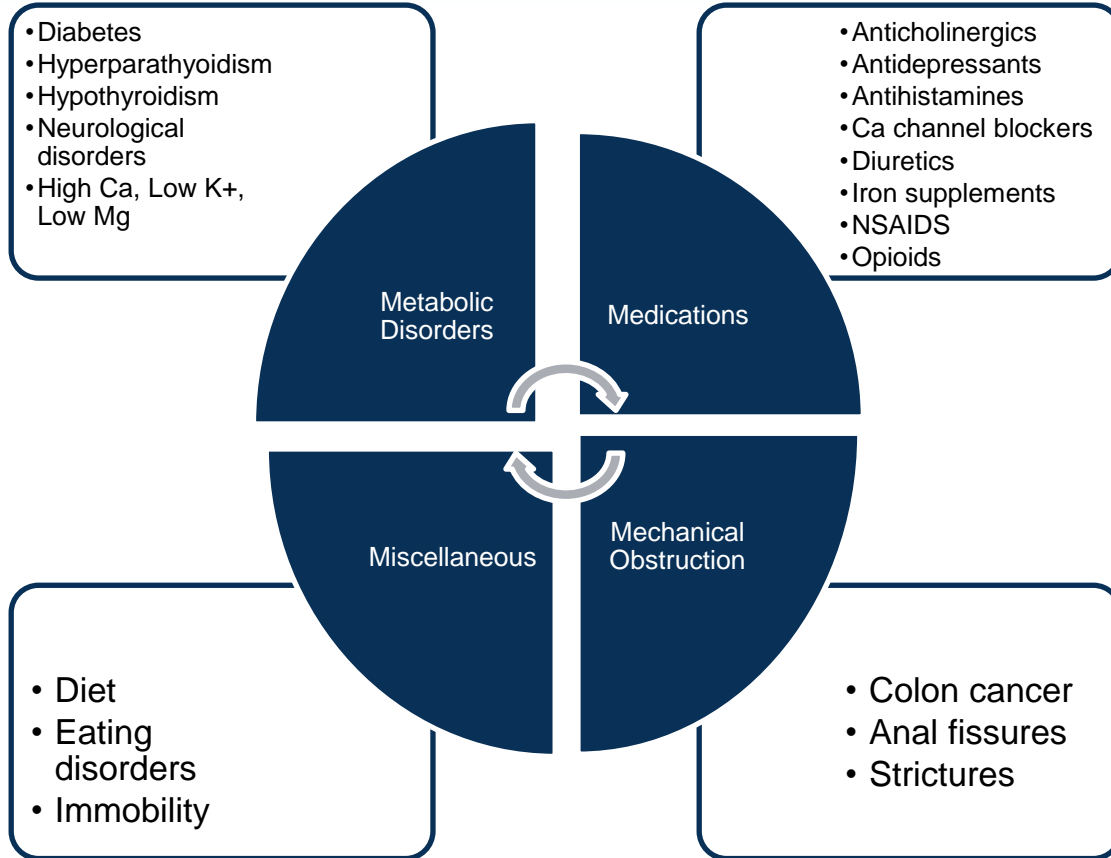
Narrowing of stools

Persistent rectal
bleeding without
anal symptoms

Family history of
colon cancer or IBD

Palpable mass

Common Secondary Causes



Results of Tests/ Labs

- **Digital Rectal Exam**: No visible hemorrhoids or excoriations, small anterior anal fissure, adequate resting tone and squeeze, adequate push effort with no paradoxical contraction noted, FOBT +
- **Labs**: CBC, CMP, TSH were normal
- **Colonoscopy**: FINDINGS: 1) 4mm polyp in transverse colon removed by cold forceps 2) 4mm rectal polyp removed by cold forceps 3) Hemorrhoids 4) Otherwise normal colonoscopy up to cecum
RECOMMENDATIONS : 1) High fiber diet 2) Follow up with endoscopist for path results and recommendations for repeat procedure
 - Path report: Transverse colon: tubular adenoma Rectal polyp: tubular adenoma

Differential Diagnosis

- Irritable bowel syndrome
- Chronic Idiopathic Constipation
- Dyssynergic Defecation

- Any further work up necessary?
- What is the diagnosis?

Results of Tests/ Labs

- **Digital Rectal Exam** and **physical exam** were unremarkable
- **Results:** CBC, CRP, celiac testing, thyroid testing (controversial) were all normal

Differential Diagnosis

- IBS-C
- CIC
- Is any further workup necessary?
- What is the diagnosis?

Rome IV IBS-C

Recurrent **abdominal pain** on average at least 1 day/week in the last 3 months, associated with two or more of the following criteria:

1. Related to defecation
 2. Associated with a change in the frequency of stool
 3. Associated with a change in the form (appearance) of stool
-

(These criteria should be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.)

Lacy BE, Mearin F, Chang L. Gastroenterology. 2016; 150(6):1393-1407.

“In practice, a clear separation between CIC and IBS with constipation may be challenging and studies have shown, not only **considerable overlap** between these entities, but also a significant **tendency for patients to migrate** between these diagnoses over time.”

Prescription Options

Medication	IBS-C	CIC
Lubiprostone	8mcg BID	24mcg BID
Linaclotide	72mcg QD, 145mcg QD	290mcg QD
Plecanatide	3mg QD	3mg QD
Tegaserod	6mg BID	X
Prucalopride	X	2mg QD, 1mg QD
Tenapanor	50mg BID	x

48-year-old female returns...

- Patient Profile: 48-yr-old woman, 7 months later
- Change in symptoms: She is having BSS 1-2 stools, every 2-3 days. Primary complaint now is abdominal discomfort most days of the week.
- What other information would you like to have?
- Which tests/labs should be offered?

Practical Approaches for IBS

- Fiber – psyllium
- PEG 3350
- Probiotics: Align
- Enteric coated peppermint oil
- Antispasmodics: dicyclomine and hyoscyamine
- Anti-gas: simethicone

Management Algorithm for IBS

Identify key patient characteristics

- Identify the predominant symptom
- Consider previous therapies, preferences and patient expectations

Educate and reassure the patient

- Name and explain the condition
- Provide reassurance

Optimize treatment

- Consider non pharmacological and pharmacological treatments based on predominant symptom, patient preference and expectations

Management Strategies IBS-C

Constipation

- Water soluble fiber
- Laxatives
- Lubiprostone
- Linaclotide
- Plecanatide

Bloating

- Lubiprostone
- Linaclotide
- Plecanatide
- Low FODMAP
- Probiotics

Pain

- Antispasmodics
- Lubiprostone
- Linaclotide
- Plecanatide
- SSRIs
- Psychological Therapy
- Probiotics

Target management at predominant symptom

ACG Monograph on Management of IBS: Diet and Lifestyle

	Rec	Quality
Suggest exercise for Overall Symptom Improvement (OSI)	Weak	Very Low
Suggest a low FODMAP diet for OSI	Weak	Very Low
Suggest <u>against</u> a gluten-free or exclusion diet based upon antibody or leukocyte activation test for OSI	Weak	Very Low
<u>Recommend</u> psyllium, but not wheat bran, for OSI	Strong	Moderate
Suggest some psychological therapies (cognitive behavioral therapy, relaxation therapy, hypnotherapy, and multicomponent psychological therapy) for OSI	Weak	Very Low

Exercise

- May be beneficial to patients with IBS
- Offers general health benefits and should be encouraged when possible



Dietary Considerations in IBS



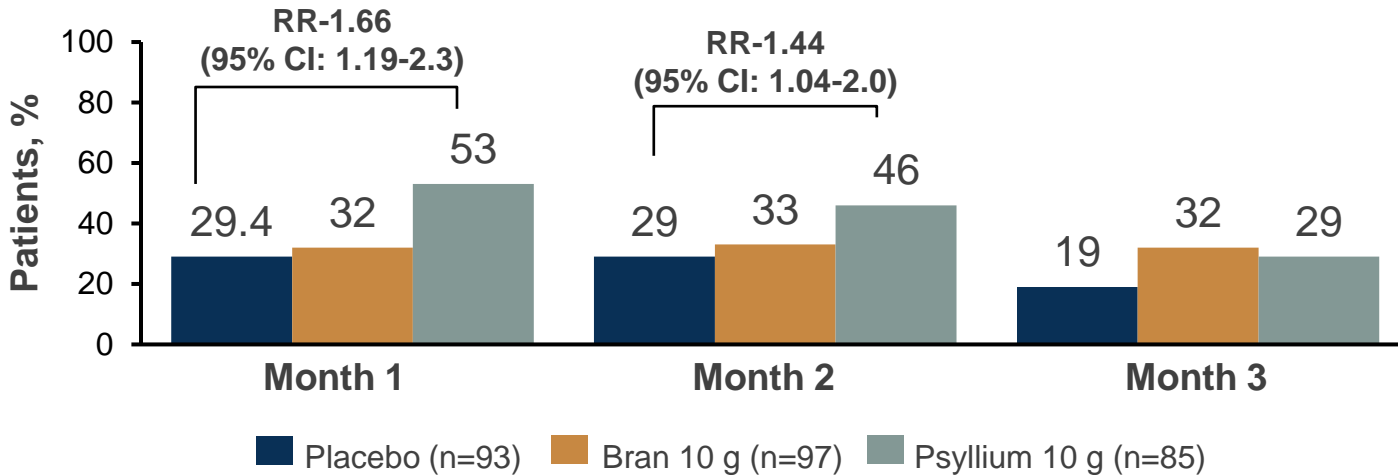
- **FODMAPS** are an important trigger of meal-related symptoms in IBS¹
- Low FODMAP diet found to improve overall symptom scores compared with typical diet in IBS patients²
- **Gluten-free** diet found to be beneficial in some patients with IBS-D^{3,4}
- Wheat contains fructans and other proteins that may also cause symptoms in IBS patients⁵
- **Food antigens** found to cause changes in the intestinal mucosa* of IBS patients that are associated with patient responses to exclusion diets⁶

*Breaks in intestinal mucosal, increased intervillous spaces, and increased intraepithelial lymphocytes demonstrated via confocal laser endomicroscopy in 22 of 36 patients with IBS.

1. Shepherd SJ et al. *Am J Gastroenterol.* 2013;108:707-717; 2. Halmos EP et al. *Gastroenterology.* 2014;146:67-75;
3. Biesiekierski JR et al. *Gastroenterology.* 2011;106:508-514; 4. Vazquez-Roque MI et al. *Gastroenterology.* 2013;144:903-911.e3;
5. Chey WD, et al. *JAMA.* 2015;313(9):949-958; 6. Fritscher-Ravens A et al. *Gastroenterology.* 2014;147:1012-1020.

Soluble or Insoluble Fiber for IBS? Primary Care Analysis

Proportion of Patients with Adequate Relief of Symptoms*



*Adequate relief defined as endpoint met 2/4 weeks of the study. Early dropout more common in the bran group.
Bijkerk CJ et al. *BMJ*. 2009;339:b3154.

Fiber in the Clinic



Dosage for IBS-C

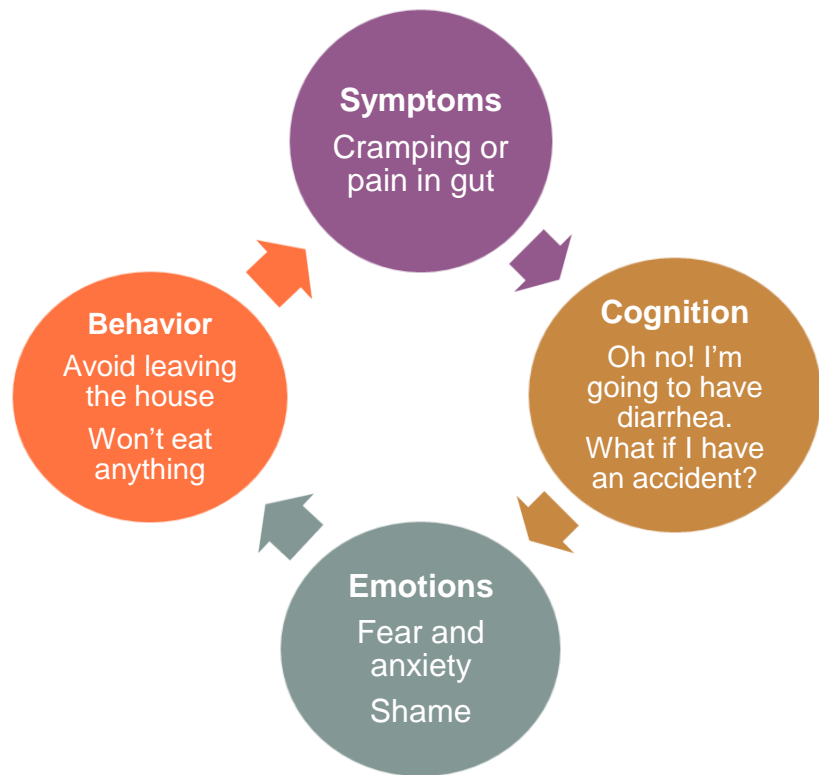
- Aim for 20 to 30 grams of fiber per day¹
- Psyllium is resistant to bacterial fermentation and retains its gel forming and water retention properties in the colon²

Administration/Other Considerations

- **Start low and go slow**¹
- Most common side effects include bloating, gas, abdominal pain, and cramping^{1,3}

1. Chey WD et al. *JAMA*. 2015;313(9):949-958;
2. Eswaran S et al. *Am J Gastroenterol*. 2013;108:718-727;
3. Suares NC, Ford AC. *Aliment Pharmacol Ther*. 2011;33:895-901.

Gut Directed Cognitive Behavioral Therapy (CBT)



- Most widely studied treatment with strongest evidence and is considered first-line treatment for patients with IBS
- CBT focuses on negative and disruptive thoughts, feelings, and behaviors related to a patient's symptoms or condition
- 6-12 therapy sessions

Hypnosis in Bowel Disorders

- Comprehensive Review of literature through January 2015
 - 24 of 35 studies (69%) focused on IBS
- More than 50% of patients unresponsive to usual medical care can be expected to benefit
- Sufficient regimen: 7 to 12 sessions, over 2 or 3 month period
- IBS symptoms (abdominal pain, constipation and diarrhea, and bloating) can be expected to improve substantially in treatment responders.
- Positive side effects
 - marked enhancement in quality of life and reduction in non-GI symptoms.
- Responders retain their improvement for years post treatment.

ACG Monograph on Management of IBS: Supplements and Medications

	Rec	Quality
Suggest <u>against</u> PEG for OSI in IBS patients.	Weak	Low
Suggest certain antispasmodics for OSI	Weak	Very Low
Suggest peppermint oil for OSI	Weak	Low
<u>Recommend</u> TCAs for OSI	Strong	High
Suggest SSRIs for OSI	Weak	Low
We suggest probiotics, taken as a group, to improve global symptoms, as well as bloating and flatulence	Weak	Low

ACG Systematic Review of Efficacy of Polyethylene Glycol in IBS



3

Clinical trials



1,582

Patients treated

There is no evidence that PEG improves overall symptoms and pain in IBS

Recommendation

Weak

Quality of evidence

Very Low

Practical Approaches

- **Antispasmodics:** otilonium, pinaverium, hyoscine, cimetropium, drotaverine, and dicyclomine¹
- **Triple-coated peppermint oil:** smooth muscle relaxant²
 - RCT of IBS-M and IBS-D (N=72): Improves the TISS* ($P<0.02$) and frequency/intensity of IBS symptoms over 4 weeks
 - AE: dyspepsia
 - Dosing: 2 capsules with meals

TISS, Total IBS Symptom Score.

1. Ford AC et al. *AM J Gastroenterol.* 2018; 113: 1-18. 2. Cash BD et al. *Dig Dis Sci.* 2016;61:560-571.

Antidepressants in IBS

Meta-analysis of 16 RCTs demonstrate that TCAs and SSRIs reduce global IBS symptoms and abdominal pain in IBS patients¹

Consider specific symptoms and side effect profile¹⁻⁴

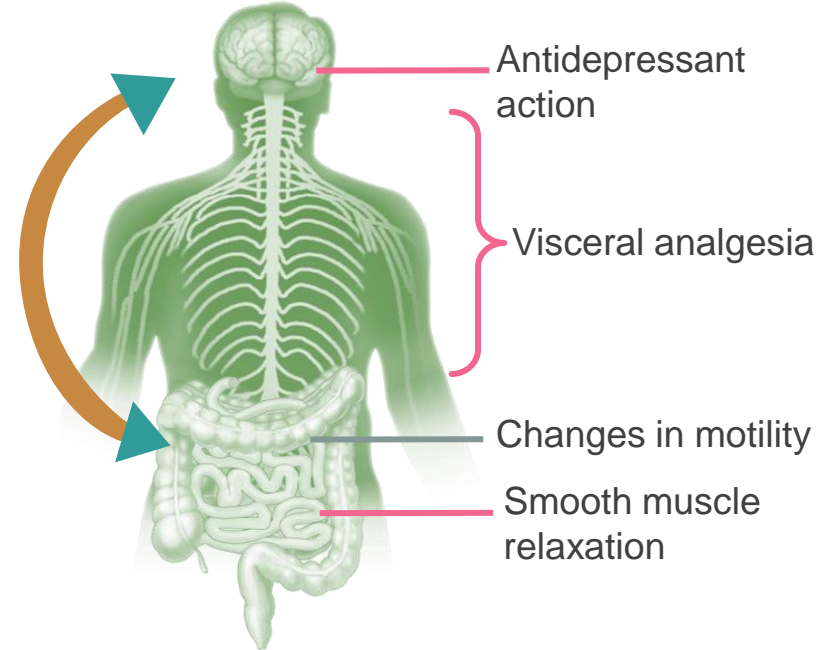
TCAs in IBS-D

SSRIs in IBS-C

SSRI for anxiety

Start with low dose and titrate slowly

Potential Antidepressant Actions in IBS³



RCTs, randomized, controlled trials; SNRIS, serotonin norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

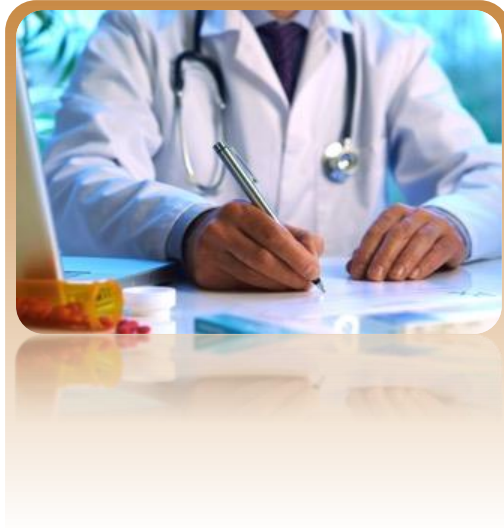
1. Ford AC et al. *Am J Gastroenterol.* 2014;109:1350-1365. 2. Grover M, Drossman DA. *Gastroenterol Clin N Am.* 2011;40:183-206. 3. Chey WD et al. *Gut Liver.* 2011;5:253-266.

4. Gorard DA, et al. *Aliment Pharmacol Ther.* 1994;8:159-166.

ACG Monograph on Management of IBS: IBS-C

	Rec	Quality
Recommend linaclotide for OSI IBS-C	Strong	High
Recommend plecanatide for OSI IBS-C	Strong	Moderate
Recommend lubiprostone for OSI IBS-C	Strong	Moderate

Linaclootide in the Clinic



Dosage for CIC

72 mcg or 145 mcg once daily

Dosage for IBS-C

290 mcg once daily

Administration

- Take on empty stomach ≥ 30 minutes before first meal of the day
- Can mix with water or applesauce for dose reduction
or patients with difficulty swallowing
- Not approved for patients < 18 years of age

*Occurring in $\geq 2\%$ of linaclootide-treated patients and at an incidence greater than placebo.

†Includes abdominal pain, upper abdominal pain, and lower abdominal pain.

LINZESS (linaclootide) [prescribing information]. Allergan USA, Inc. Irvine, CA; 2017

Linaclootide Adverse Events



Common GI Adverse Events in IBS-C and CIC Trials*

Adverse Event	IBS-C		CIC	
	PBO n=798	LIN 290 mcg n=807	PBO n=423	LIN 145 mcg n=430
	%			
Diarrhea	3	20	5	16
Abdominal pain†	5	7	6	7
Flatulence	2	4	5	6
Abdominal distension	1	2	2	3

There is a risk of serious dehydration in pediatric patients. If severe diarrhea occurs, dosing should be suspended and the patient rehydrated.

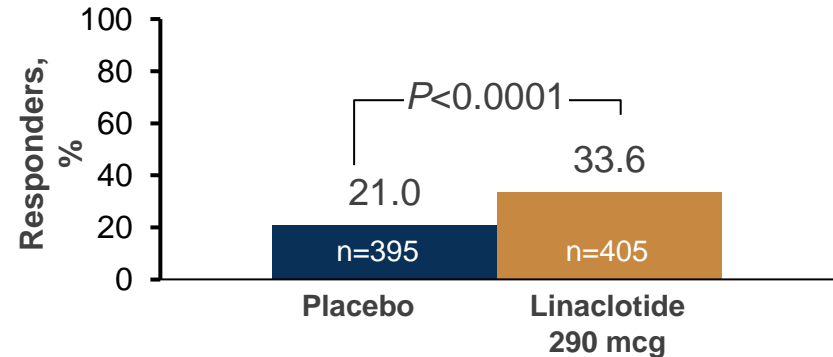
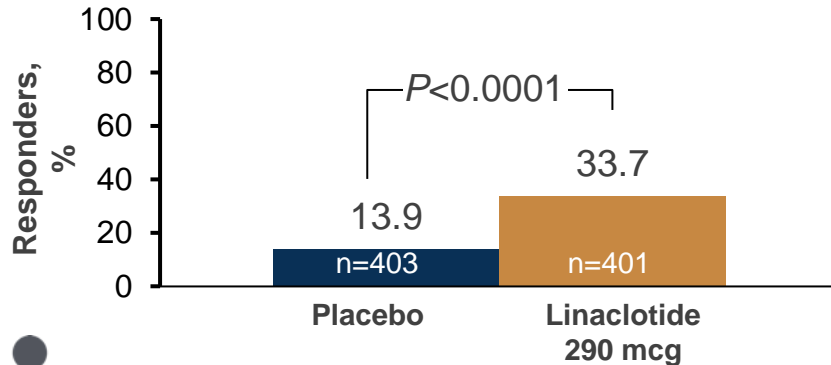
*Occurring in $\geq 2\%$ of linaclootide-treated patients and at an incidence greater than placebo.

†Includes abdominal pain, upper abdominal pain, and lower abdominal pain.

LINZESS (linaclootide) [prescribing information]. Allergan USA, Inc. Irvine, CA; 2017

Linaclootide Significantly Improves Abdominal Pain and Bowel Symptoms Associated with IBS-C

FDA Composite Endpoint (primary endpoint) in Linaclootide Pivotal Trials^{1,2}



Linaclootide significantly improves abdominal pain and bloating¹

FDA-Defined Endpoint

Each week, $\geq 30\%$ decrease in **worst abdominal pain** + increase ≥ 1 **CSBM** from baseline for ≥ 6 of 12 weeks.

CSBM, complete spontaneous bowel movement.

1. Chey W et al. *Am J Gastroenterol.* 2012;107:1714-1724; 2. Rao S et al. *Am J Gastroenterol.* 2012;107:1714-1724.

Plecanatide in the Clinic



**Dosage for CIC
and IBS-C**
3 mg once daily

Common GI Adverse Events in CIC/IBS-C Trials*

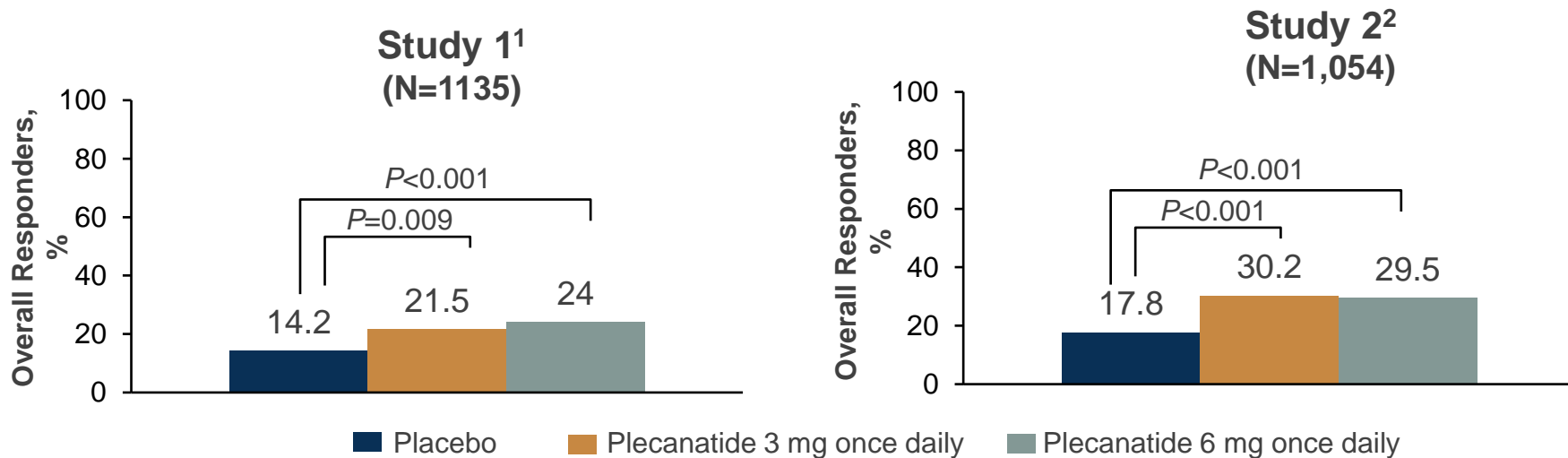
Adverse Events	CIC		IBS-C	
	Placebo n=870	Plecanatide 3 mg n=863	Placebo n=726	Plecanatide 3 mg n=723
	%		%	
Most common Aes* Diarrhea	1	5	1	4.3
Severe diarrhea	0.3	0.6	0.1	1
Discontinuation due to diarrhea	0.5	2	0	1.2

Diarrhea occurred within the first 3 days of treatment. There is a risk of serious dehydration in pediatric patients. If severe diarrhea occurs, dosing should be suspended and the patient rehydrated.

*Occurring in $\geq 2\%$ of plecanatide-treated patients and at an incidence greater than placebo.
Trulance (plecanatide) [prescribing information]. Synergy Pharmaceuticals Inc. New York, NY; 2018.

Plecanatide for IBS-C: Phase 3 Efficacy Results

Overall Responders During 12 Weeks*



*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.

Lubiprostone in the Clinic



Dosage for CIC
24 mcg BID

Dosage for IBS-C
8 mcg BID

Administration
Take with food and water
to minimize nausea

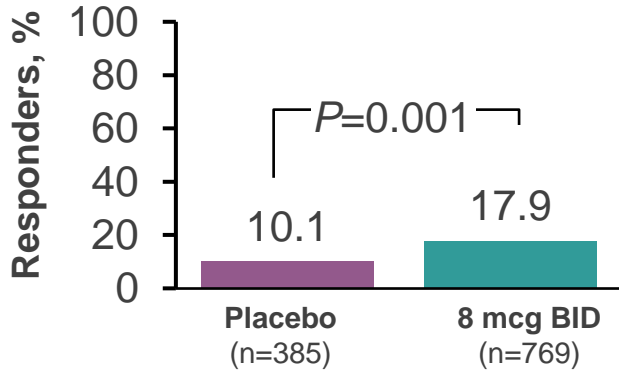
Common GI Adverse Events in IBS-C and CIC Trials*

Adverse Events	IBS-C		CIC	
	PBO n=435	LUB 8 mcg BID n=1011	PBO n=316	LUB 24 mcg BID n=1113
	%			
Nausea	4	8	3	29
Diarrhea	4	7	1	12
Abdominal pain	5	5	3	8
Abdominal distension	2	3	2	6

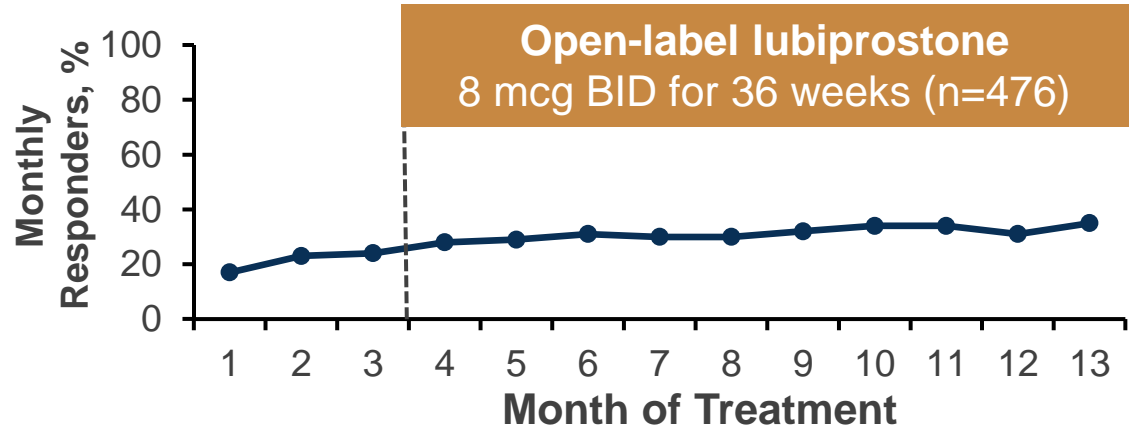
*Includes only those events associated with treatment (possibly or probably related, as assessed by investigator)
Amitiza (lubiprostone) [prescribing information]. Sucampo Pharma Americas, LLC; Bethesda, MD; 2018.

Lubiprostone for IBS-C

Overall Responders at 12 Weeks*¹



Monthly Responder Rates in Randomized Withdrawal/Extension Studies²



Lubiprostone significantly improves abdominal pain and bloating^{1,2}

*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.

Note: Lubiprostone is FDA-approved for treatment of IBS-C in women ≥ 18 years of age.

1. Drossman DA et al. *Aliment Pharmacol Ther.* 2009;29:329-341; 2. Chey WD et al. *Aliment Pharmacol Ther.* 2012; 35:587-599.

Tegaserod

- Serotonin type-4 (5-HT₄) receptor agonist
- Indicated for treatment of adult women less than 65 years of age with IBS-C
- The approval to reintroduce ZELNORM came after a thorough safety review by the FDA and an FDA-assembled Gastrointestinal Drugs Advisory Committee (GIDAC).

Tegaserod in the Clinic



Dosage for IBS-C

6 mg taken twice daily

Administration

- 30 minutes before meals
- adult women less than 65 years of age
- safety and effectiveness of ZELNORM in men with IBS-C have not been established

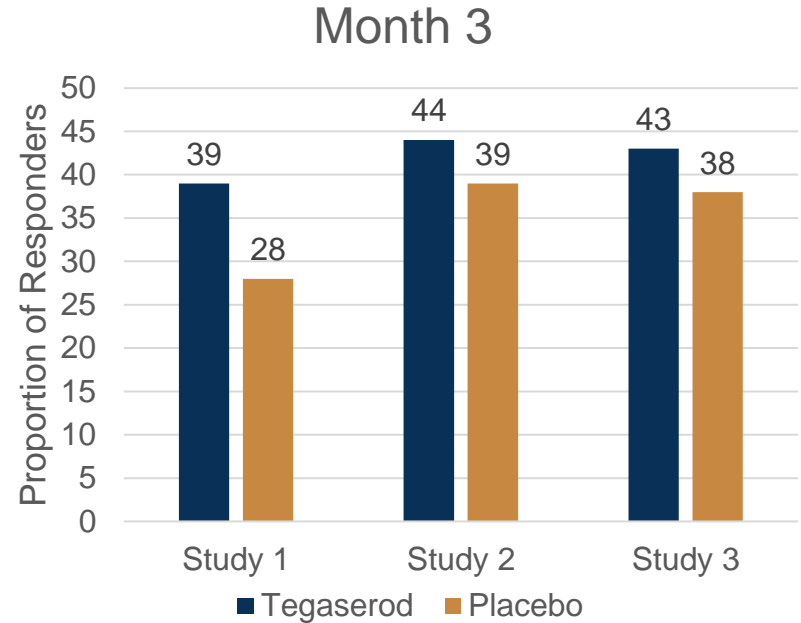
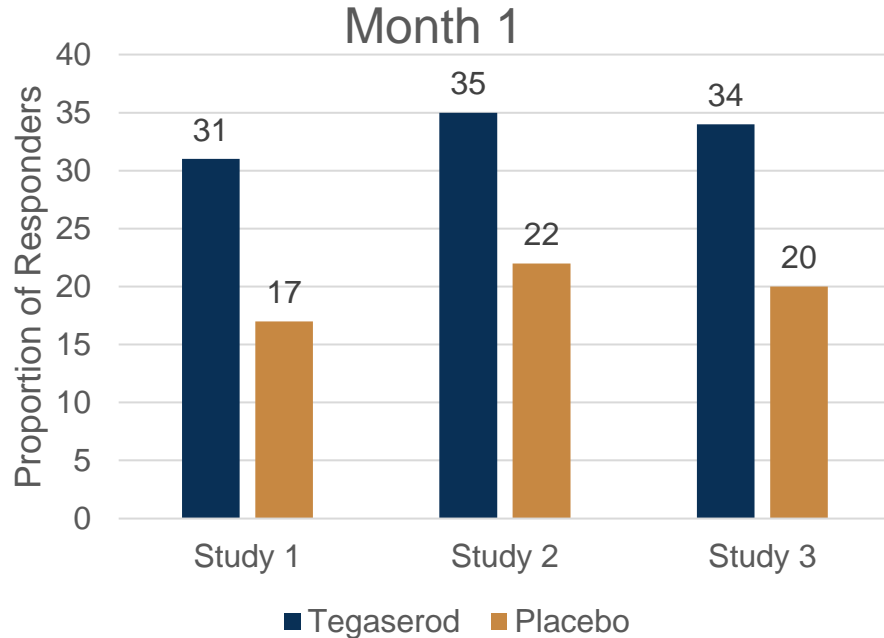
Contraindications

- A history of myocardial infarction, stroke, transient ischemic attack, or angina.
- A history of ischemic colitis or other forms of intestinal ischemia.
- Severe renal impairment (eGFR < 15 mL/min/1.73 m²) or end-stage renal disease.
- Moderate or severe hepatic impairment (Child-Pugh B or C).
- A history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions
- Hypersensitivity to tegaserod.

Adverse reactions (>2%)

Headache, abdominal pain, nausea, diarrhea, flatulence, dyspepsia, and dizziness.

Tegaserod: Efficacy Responder Rates in 3 Placebo Controlled Trials



Tegaserod in the Clinic

- Major Adverse Cardiovascular Events (MACE): The potential risks of treatment must be balanced with expectations in improvements in symptoms of IBS-C. Discontinue ZELNORM treatment in patients who experience a myocardial infarction, stroke, transient ischemic attack or angina. (4) Evaluate the risks and benefits of continued treatment in patients who develop clinical or other evidence of cardiovascular ischemic heart disease and/or experience changes in health status that could increase cardiovascular risk during treatment.
- Ischemic Colitis: Monitor for rectal bleeding, bloody diarrhea, and new or worsening abdominal pain and discontinue ZELNORM if symptoms develop.
- Volume Depletion Associated with Diarrhea: Avoid use in patients with severe diarrhea. Instruct patients to discontinue ZELNORM and contact their healthcare provider if severe diarrhea, hypotension or syncope occur.
- Suicidal Ideation and Behavior: Monitor patients for clinical worsening of depression and emergence of suicidal thoughts and behaviors, especially during the initial few months of treatment. Instruct patients to immediately discontinue ZELNORM and contact their healthcare provider if their depression is persistently worse or they are experiencing emergent suicidal thoughts or behaviors.

Tenapanor in the Clinic



Dosage for IBS-C

50 mg taken twice daily

Administration

Immediately before breakfast and dinner

Contraindications

- Children <6 years of age
- Known or suspected mechanical obstruction

Adverse reactions (>2%)

Diarrhea (15-16%), severe diarrhea (2.5%), abdominal distention, flatulence, dizziness

Patient Follow-Up

- What would your follow up plan be?



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Q&A