IBS Centers of Educational Expertise™

A Complicated Case of Refractory Constipation: When is Surgery an Option?

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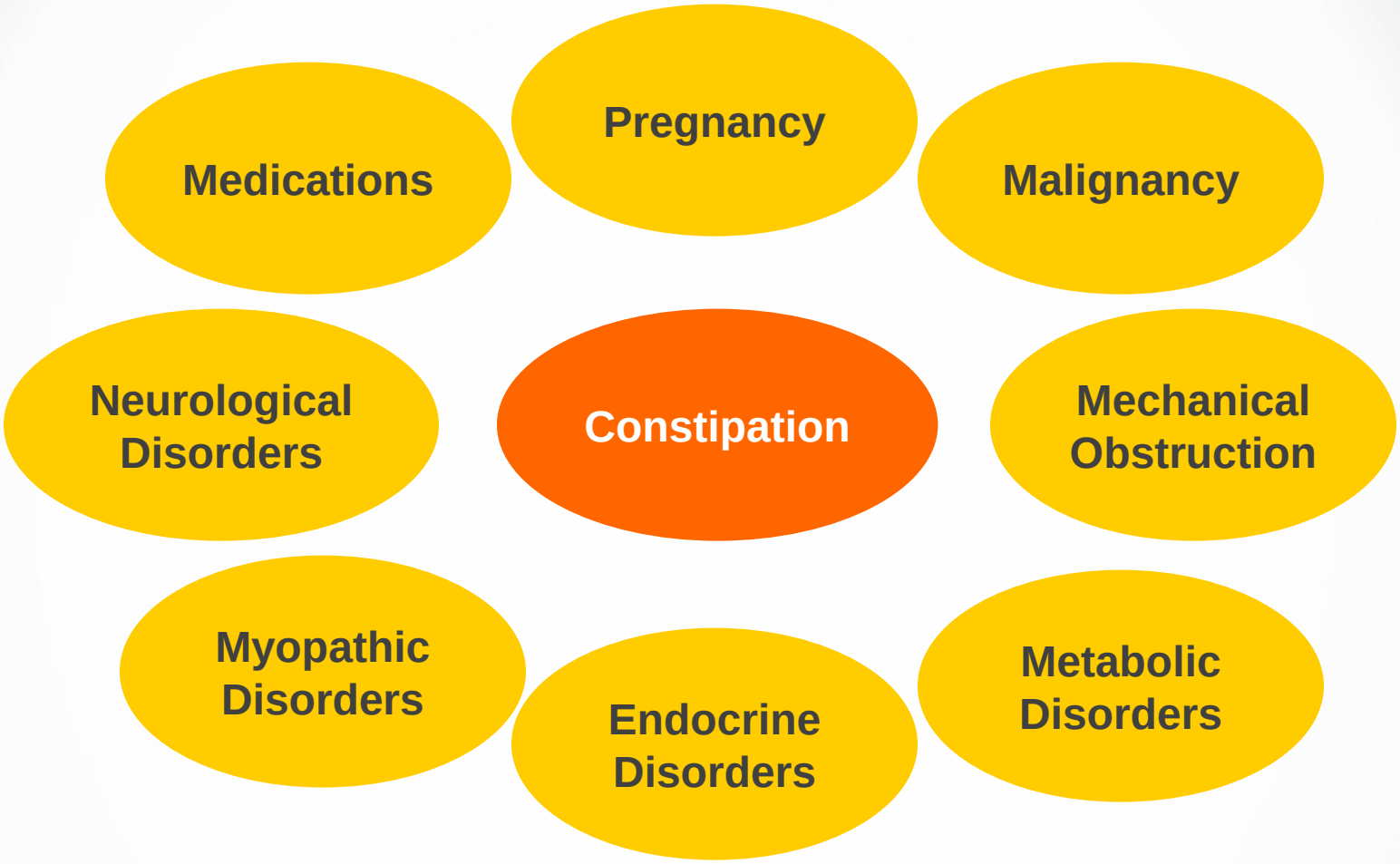
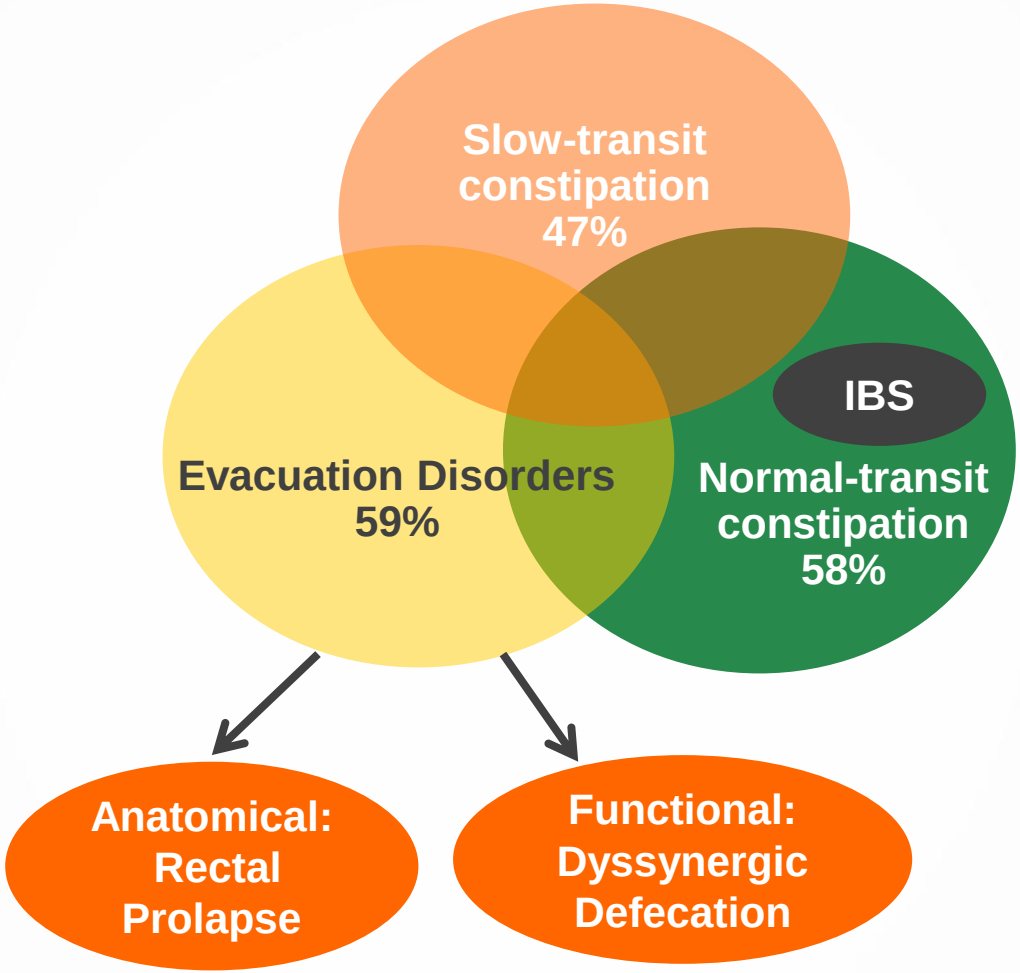
Secondary Causes of Constipation



Subtypes of Primary Constipation



Mertz H et al. *Am J Gastroenterol*. 1999;94:609-614; Rao SS et al. *Am J Gastroenterol* 2005;100:1605-1615.

Symptoms Underlying Mechanisms of Constipation

Symptoms Suggesting Slow Transit	Symptoms Suggesting Evacuation Problems
Infrequent bowel movements	Inability to evacuate soft stool/enemas
Bloating	Excessive straining
Lack of urge to defecate	Incomplete evacuation
Stool form (Bristol Stool Scale)	Manual maneuvers to facilitate defecation

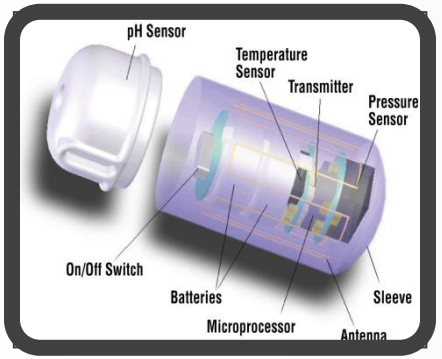
- No symptom specific enough to differentiate constipation subtypes
- Objective testing necessary

Koch A et al. *Dis Colon Rectum.* 1997;40:902-906

What Tests Assess Colonic Transit/Function?

- Radioopaque marker (ROM) studies
- Wireless ambulatory pH/motility capsule
- Scintigraphy

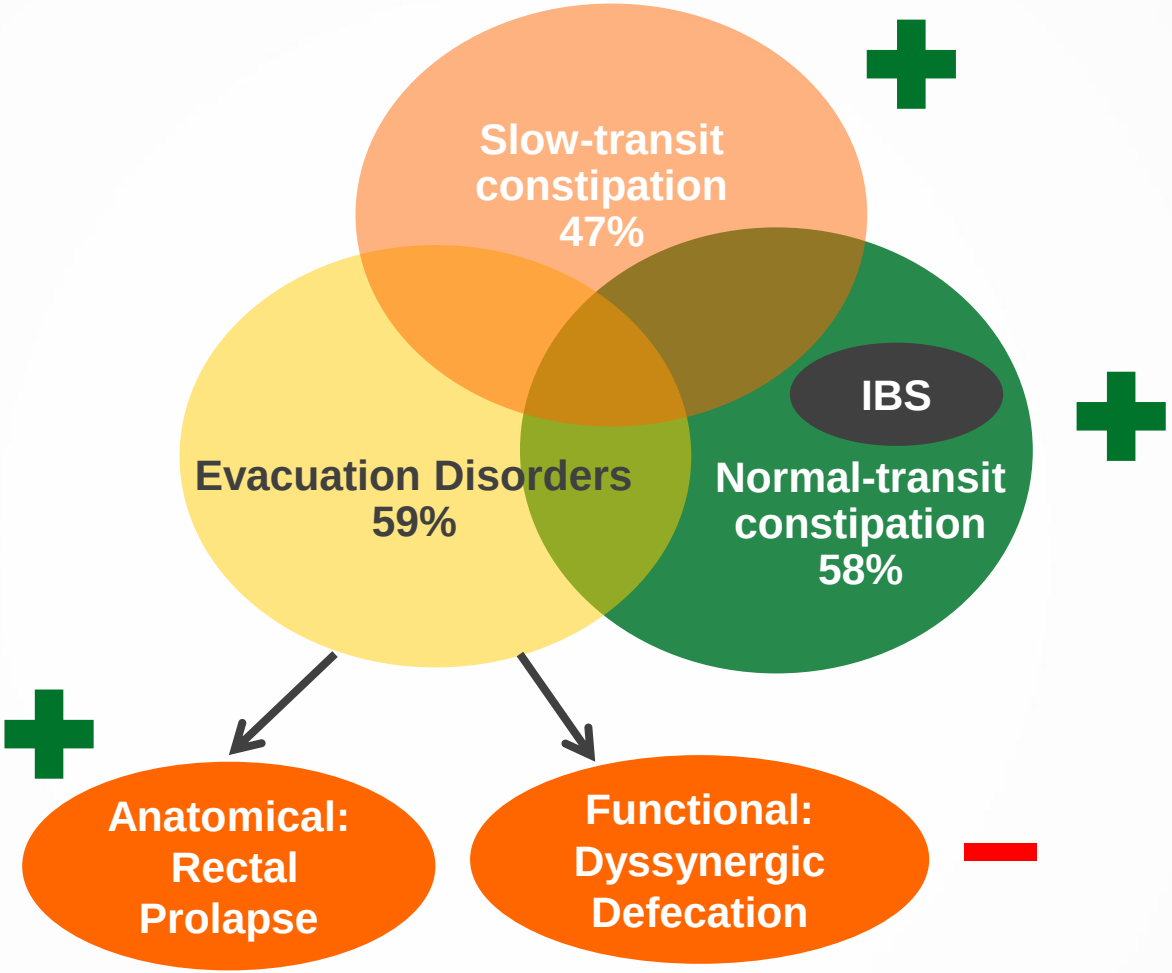
- Colonic manometry



- Anorectal manometry (ARM)
- Balloon Expulsion (BET)
- Barium/MRI defecography

Rao SSC et al. *Am J Gastroenterol*. 2005;100:1605-1615.
Brandt LJ et al. *Am J Gastroenterol*. 2005;100(suppl 1):S5-S21.
Rao SSC. *Gastroenterol Clin North Am*. 2003;32:659-683.

Subtypes of Primary Constipation



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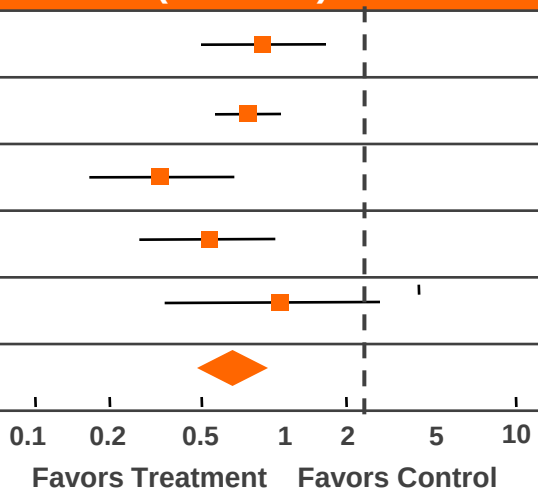
Efficacy of SSRIs in Relieving Global IBS Symptoms

Study (Year, Drug, Dose)	Treatment n/N	Control n/N	RR (Random) 95% CI
Kuiken (2003, fluoxetine 20 qd)	9/19	12/21	
Tabas (2004, paroxetine 10-40 qd)	25/44	36/46	
Vahedi (2005, fluoxetine 20 qd)	6/22	19/22	
Tack (2006, citalopram 20-40 qd)	5/11	11/12	
Talley (2008, citalopram 40 qd)	5/17	5/16	
Subtotal (95% CI)	**113**	**117**	



RR=0.62
(95% CI=0.45-0.87)

Note: SSRIs are not FDA-approved for IBS

CI=confidence interval; RR=relative risk; SSRI=selective serotonin reuptake inhibitor

Ford AC et al. *Gut*. 2009;58:367-378.

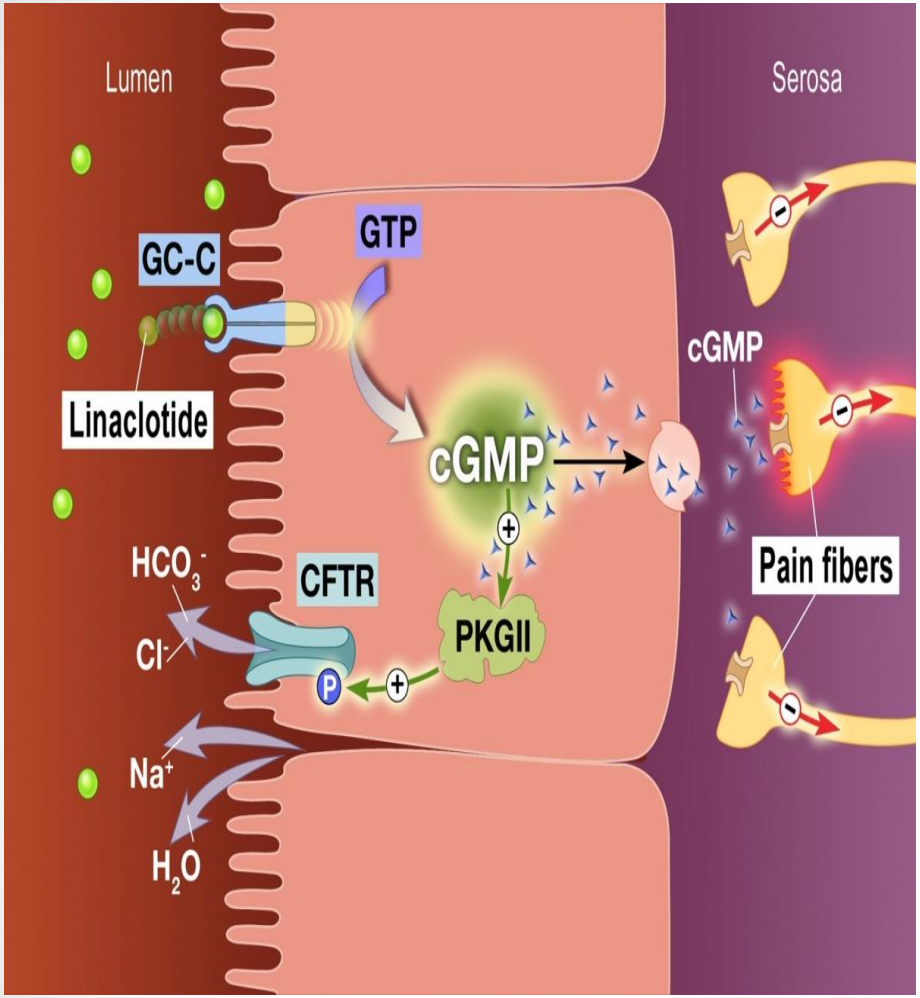
IBS: Psychosocial Therapies

Treatment Modality	Studies (n)	N		RR (95% CI)
		Patients	Controls	
Cognitive behavioral therapy	7	279	212	0.60 (0.42-0.87)
Hypnotherapy	2	20	20	0.48 (0.26-0.87)
Multicomponent psychological therapy	4	106	105	0.69 (0.56-0.86)
Dynamic psychotherapy	2	138	135	0.60 (0.39-0.93)
Stress management	1	18	17	0.34 (0.16-0.73)

RR=relative risk

Ford AC et al. *Gut*. 2009;58:367-378.

Linaclotide



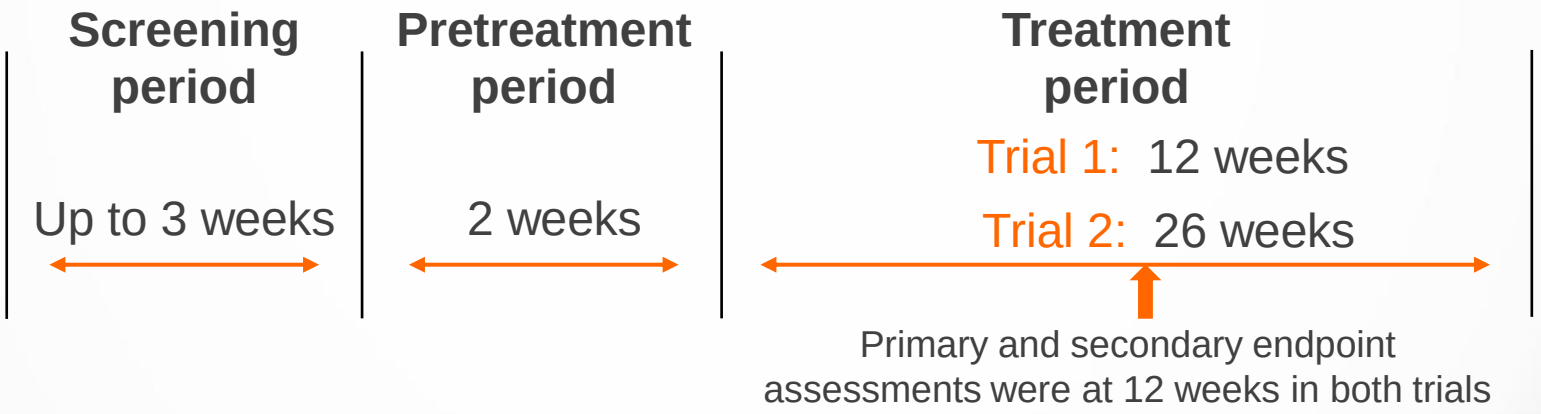
- **Guanylate cyclase-C (GC-C) agonist, results in generation of cyclic guanosine monophosphate (cGMP)**
- **Based upon available preclinical data, cGMP is proposed to have two activities:**
  - **Intracellular:** activation of CFTR→ increased luminal fluid secretion & intestinal transit
  - **Extracellular:** inhibition of pain fiber activity→ reduced visceral pain
- **2 Phase III Trials for IBS-C**

CFTR=cystic fibrosis transmembrane conductance regulator

Forte LR Jr. *Pharmacol Ther* 2004;104:137-162.
Anderson V et al., *Gastroenterology* 2007;133:761-768.

Linaclotide Phase 3 IBS-C Trials

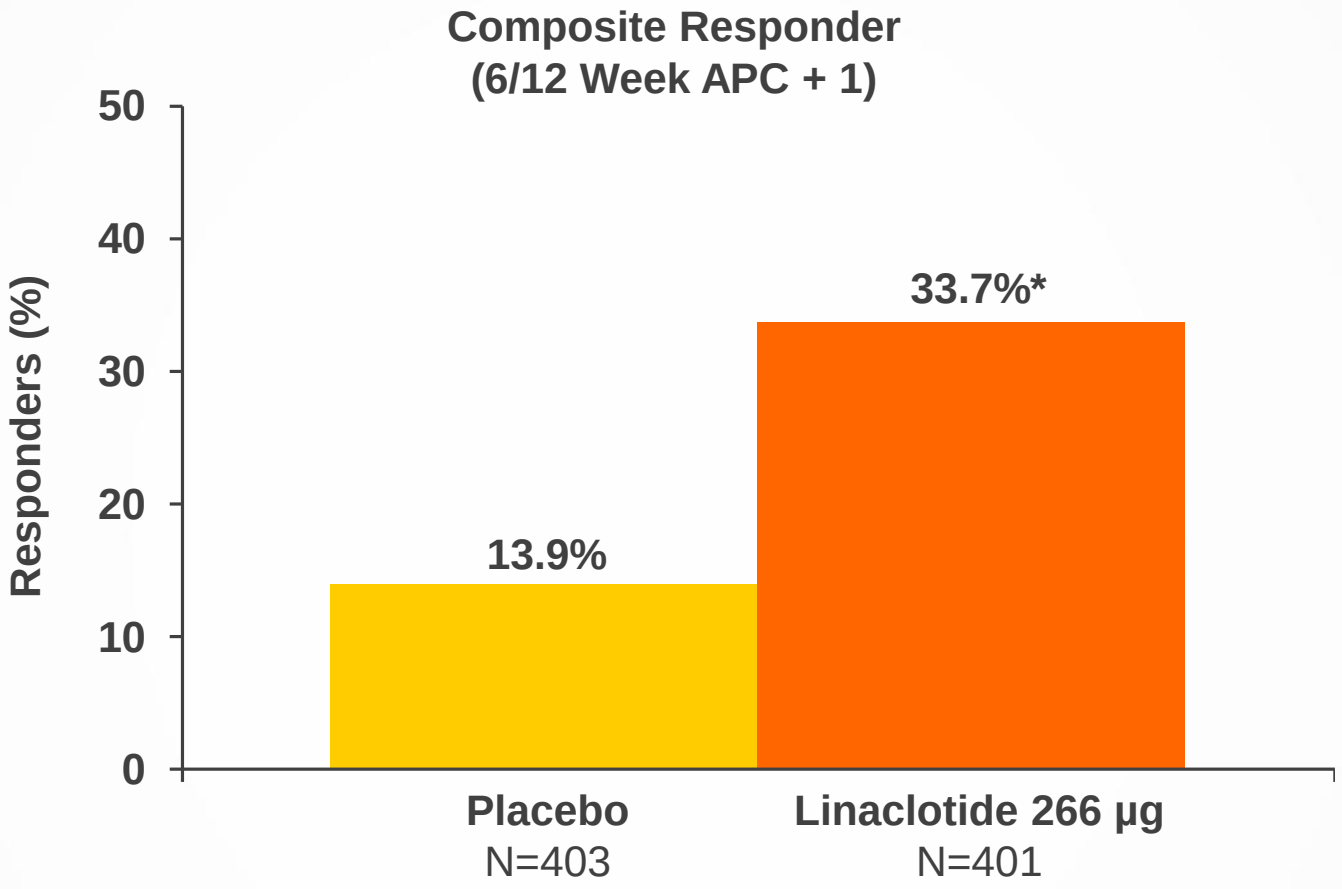
- **Trial Design**: 2 randomized, double-blind, placebo-controlled, parallel-group, multicenter trials
- **Population**: 1604 patients (90% female) Modified Rome II; 2-week baseline period had <3 CSBM/wk, ≤5 SBM/wk, abdominal pain ≥3 on 0–10 point scale
- **Treatment Groups**: placebo, linaclotide (LIN) 266 µg oral capsule daily
- **Endpoints**: Responder endpoints assessed *a priori* at 12 weeks



CSBM=complete spontaneous bowel movement; SBM=spontaneous bowel movement

Rao SSC et al. DDW 2011. Abstract no. 845; Chey W et al. DDW 2011. Abstract no. 837.

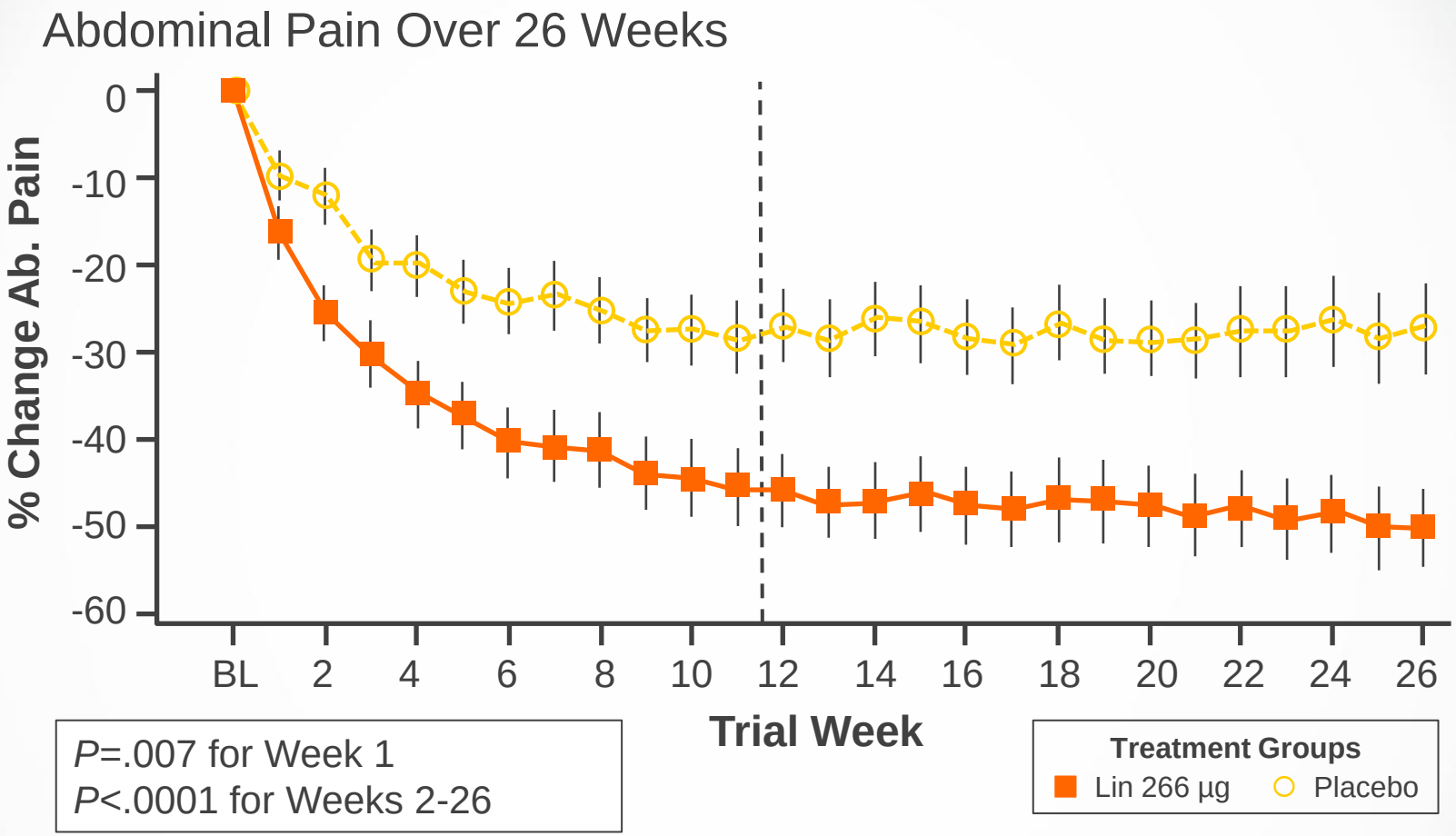
Linaclotide Phase 3 IBS-C Trial



****P*<.0001, ITT population**

Chey W et al. DDW 2011. Abstract no. 837

Linaclotide for IBS-C: Trial II

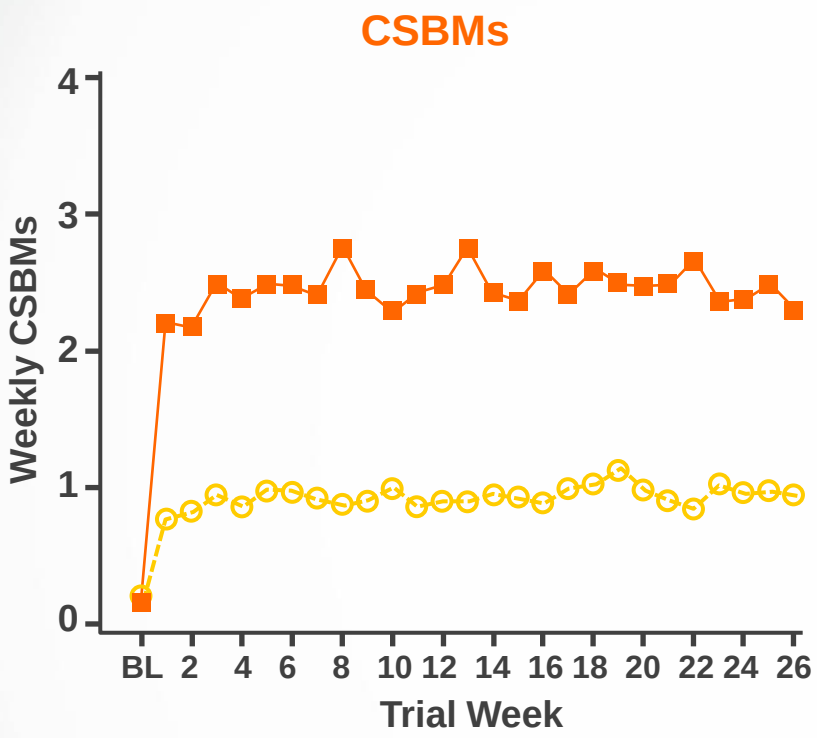


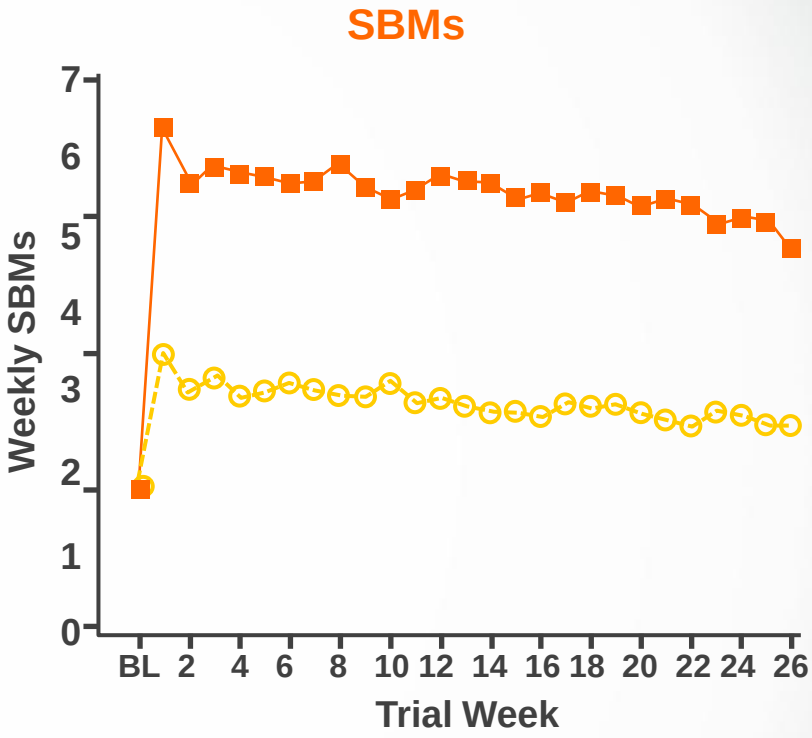
Data not shown: Similar results for bloating, straining across all 26 weeks; *P*<.0001

Chey W et al. DDW 2011. Abstract no. 837.

Linaclotide for IBS-C: Trial II

SBMs and CSBMs Over 26 Weeks:





Treatment Groups
■ 266 µg ○ Placebo

P<.0001 for each of the 26 Weeks in the treatment period for both SBMs and CSBMs

Chey W et al. DDW 2011. Abstract no. 837.

Linaclotide IBS-C Trials I & II: THPs

- Across both trials significant improvements in primary and secondary endpoints at 12 weeks
- Responses sustained at 26 weeks for primary endpoints and abdominal pain/bloating/straining/CSBM/SBMs improved across all weeks of the trial
- Adverse events minimal: Diarrhea most common
  - 4-6% linaclotide
  - 0.2-0.3% placebo

Rao SSC et al. DDW 2011. Abstract no. 845. Chey W et al. DDW 2011. Abstract no. 837.