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Current Pharmacological Treatment Options in Chronic Constipation and IBS with Constipation

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Learning Objectives

- To review the treatments currently available for chronic constipation and IBS-C
- To differentiate treatments based on their mechanism of action
- To discuss how to tailor treatments to the individual patient

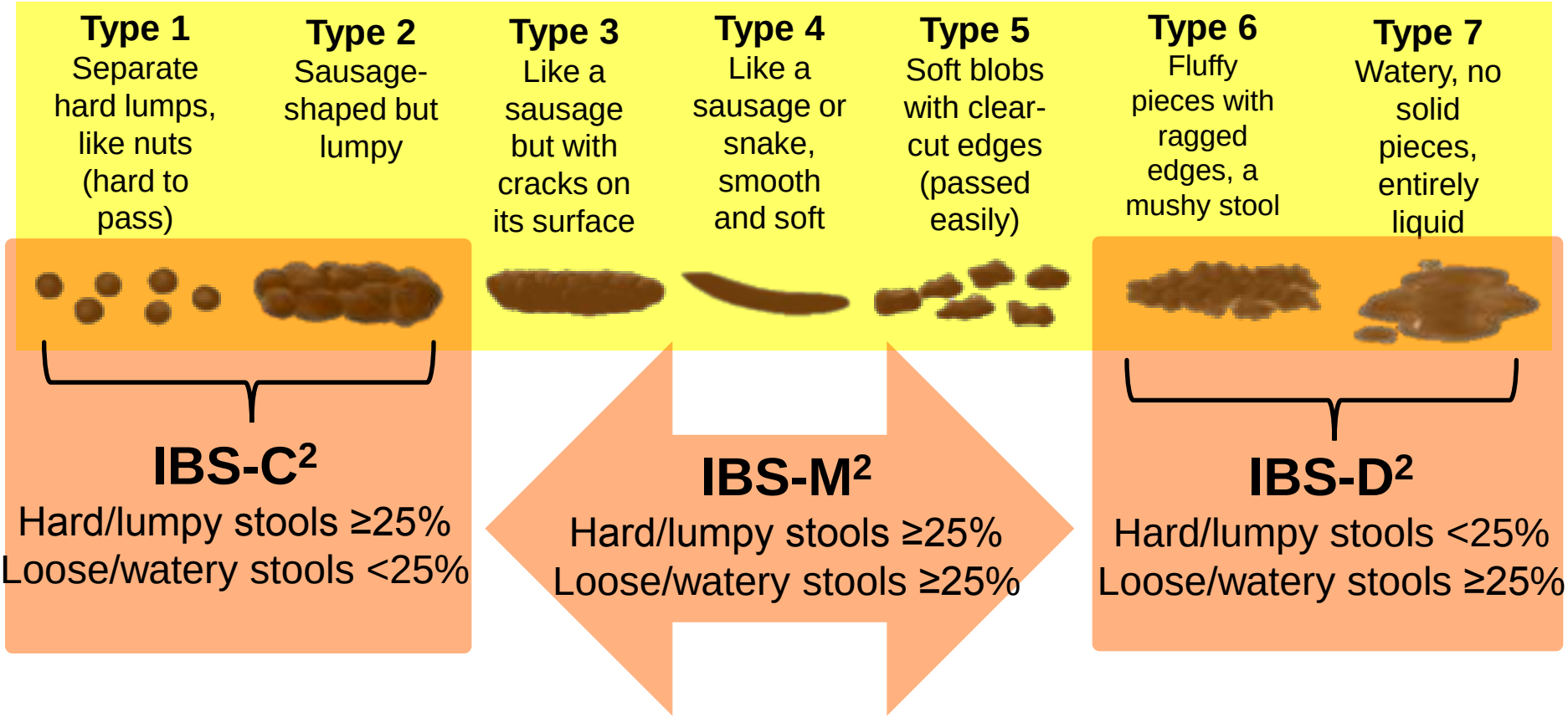
Rome III Criteria*: IBS-C

- Recurrent abdominal pain or discomfort at least 3 days/month associated with two or more of the following:
  - Improvement with defecation
  - Onset associated with a change in the frequency of stool
  - Onset associated with a change in the form of stool

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

Longstreth GF et al. *Gastroenterology*. 2006; 130:1480

IBS-C Subtype is Based on Stool Form



IBS-C=constipation-predominant IBS; IBS-D=diarrhea-predominant IBS; IBS-M=mixed IBS; IBS-U=unsubtyped IBS.

O'Donnell LJD et al. *BMJ*. 1990;300:439-440.
Longstreth GF, et al. *Gastroenterology.* 2006;130:1480-1491.

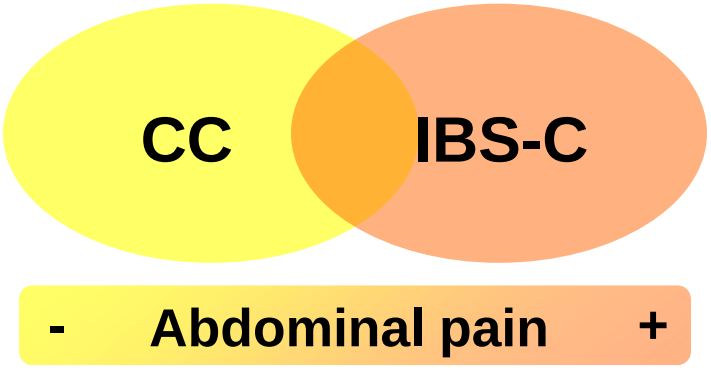
Rome III: Chronic Constipation (CC)

- ≥2 of the following for ≥12 weeks out of the last 12 months
  - Straining
  - Lumpy or hard stools
  - Sensation of incomplete evacuation
  - Sensation of anorectal obstruction or blockage
  - Manual maneuvers to facilitate defecation
  - < 3 BMs/wk

  >25% of defecations
- Loose stools are rarely present without laxatives. Do not meet criteria for IBS

Longstreth GF, et al. *Gastroenterology*. 2006;130:1480-1491.

Symptoms of Chronic Constipation Overlap with IBS-C



<3 BMs / week	+++	+++
Hard / lumpy stools	+++	+++
Straining	+++	+++
Feeling of incomplete evacuation	+++	+++
Bloating / abdominal distension	++	+++

Drossman et al, *Gastroenterology* 1997; 112: 2120–37
Thompson et al, *Gut* 1999; 45(Suppl. 2): II43–7
Brandt et al, *Am J Gastroenterol* 2005; 100(Suppl. 1): S5–S21

Graded Treatment for Patients with IBS-C and CC

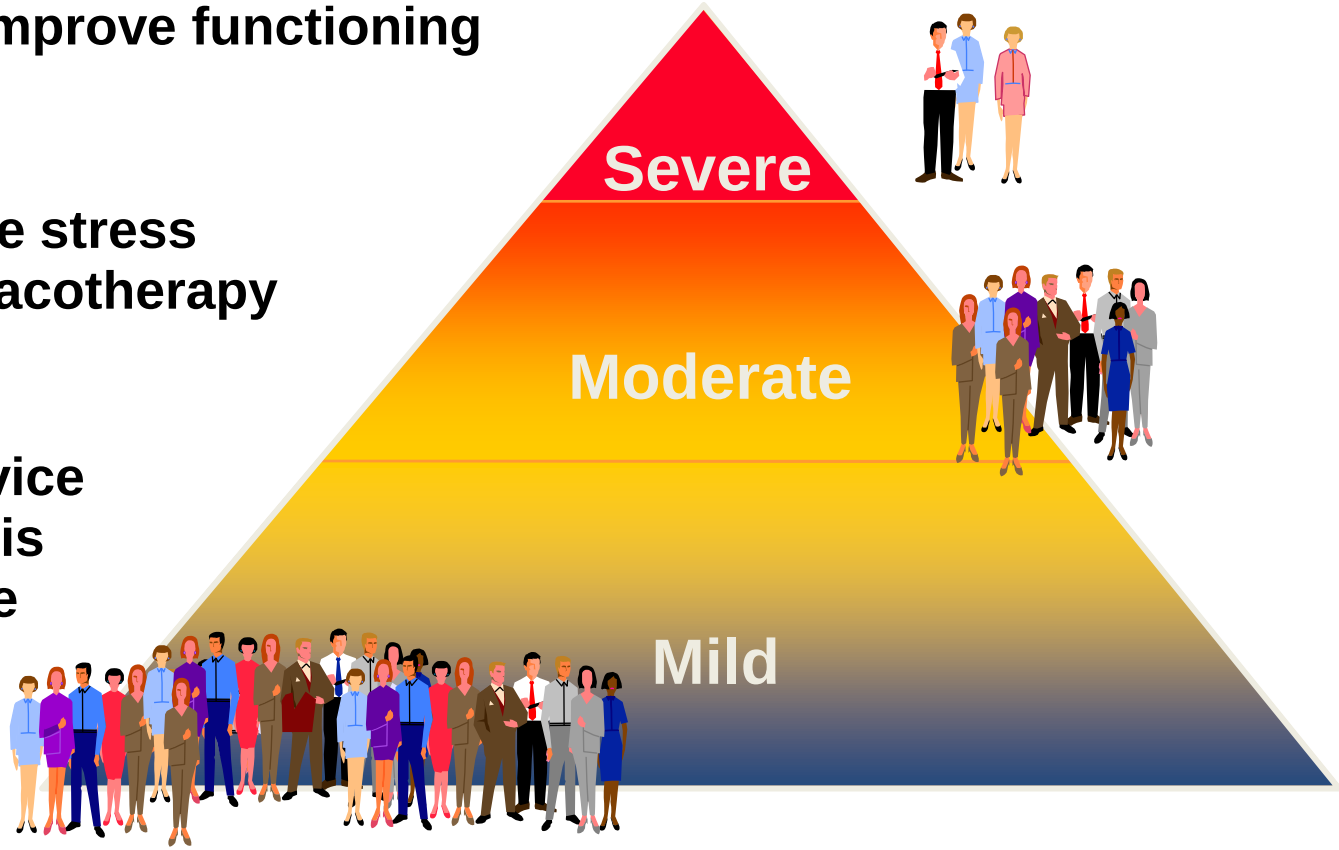
- **Multidisciplinary approach**
- **Psychological treatments**
- **Improve functioning**

+

- **Manage stress**
- **Pharmacotherapy**

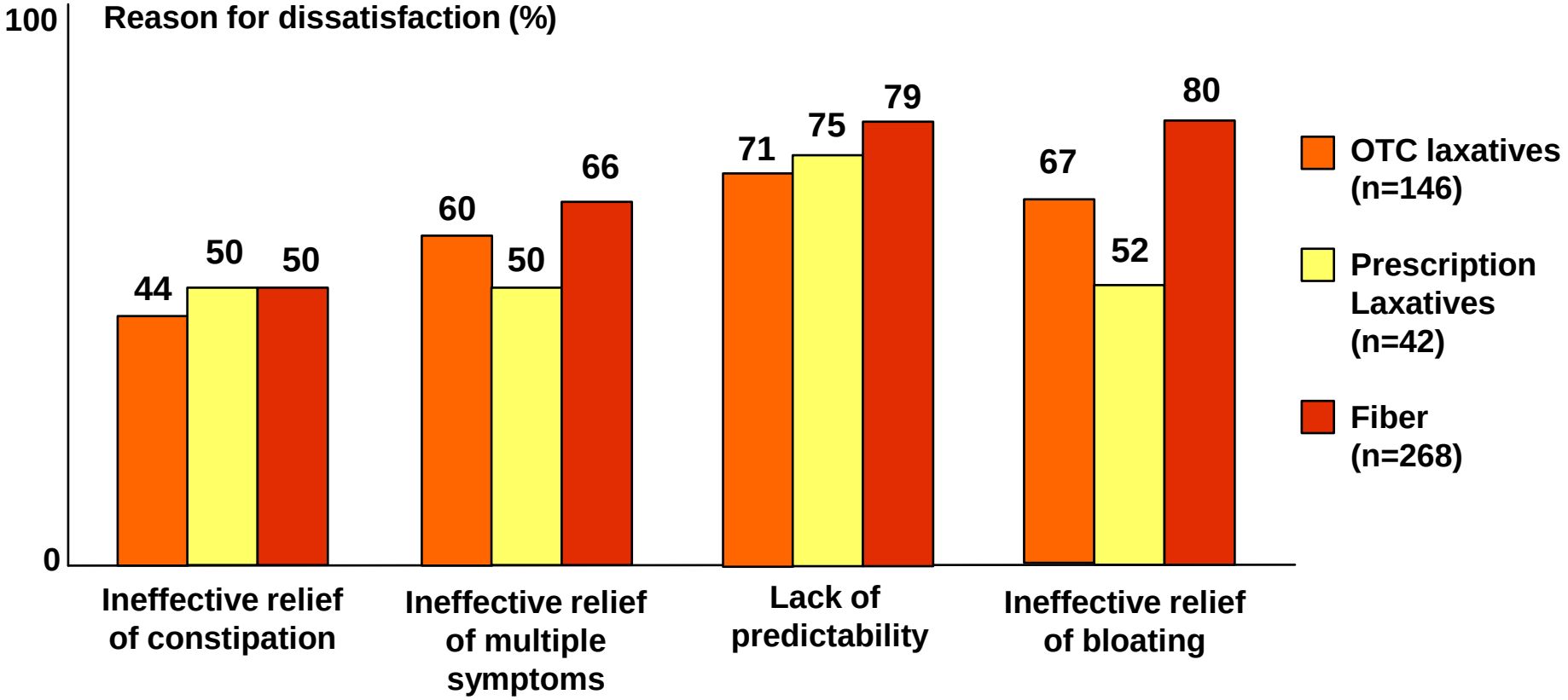
+

- **Diet, lifestyle advice**
- **Positive diagnosis**
- **Explain, reassure**



Reasons for Dissatisfaction with Traditional Constipation Treatments

- 557 patients surveyed; 47% not completely satisfied with their constipation relief therapy



Johanson & Kralstein, *Aliment Pharmacol Ther* 2007; 25: 599–608

ACG Task Force Recommendations: IBS-C

	Improvements in Symptoms					Grading Recommendations*	
	Global Symptoms	Pain	Bloating	Stool Frequency	Stool Consistency	Recommendation	Quality
Fiber (psyllium)				+	+	2	C
Laxatives				+		2 (PEG)	C
Lubiprostone	+	+			+	1	B
Antidepressants	+	+				1	B
Tegaserod†	+	±	+	+	+	2	A

*Recommendations–based on the balance of benefits, risks, burdens, and sometimes cost: Grade 1=strong, Grade 2=weak; Assessment of Quality of evidence–according to the quality of study design, consistency of results among studies, directness and applicability of study endpoints: Grade A=high, Grade B=moderate, Grade C=low.

†Available only under Emergency IND program; PEG=polyethylene glycol.

Adapted from ACG Task Force on IBS. *Am J Gastroenterol*. 2009;104(suppl 1):S1-S35.

ACG Task Force Recommendations: CC

Type of laxative	Examples	Efficacy	Recommendation
Bulk laxatives	Psyllium, methylcellulose	**Psyllium increases stool frequency and consistency**	B (Psyllium)
Stool softeners	Docusate sodium mineral oil	**Less effective than psyllium for increasing BM frequency** **no evidence to support use in CC**	B
Stimulant laxatives	Senna, bisacodyl	**May be effective when given acutely for short periods**	B
Osmotic laxatives	PEG, lactulose, magnesium compounds	**PEG effective in constipation** **Magnesium compounds**	A (PEG, lactulose) B (Magnesium)

Lubricants, alternative, herbs, combination all received a C recommendation due to the lack of controlled trials
Note: Lubiprostone was not included in the Task Force's recommendation

Brandt et al, *Am J Gastroenterol* 2005; 100: S5–S21
Ramkumar & Rao, *Am J Gastroenterol* 2005; 100: 936–71

Fiber

- Each gram fiber = 2.7 grams of stool
- In non-constipated adults dietary fiber:
  - increases stool weight and frequency of defecation
  - decreases colonic transit time
- Bloating, distention, cramps are common. Over 50% of patients do not continue therapy!

Muller-Lissner SA et al *Br Med J* (Clin Res Ed) 1988; 296:615-7.
Cummings JH et al *Postgrad Med J* 1984; 60:811-9

Systematic Review: Fiber in CC

Study	Fiber	Criteria used to define response to therapy	N	Treatment effect in fiber arm	Treatment effect in placebo/no therapy arm
Fenn	Psyllium	Improvement in global symptoms	211	86.5%	47.4%
Ashraf	Psyllium	Increase in mean stool frequency per week	22	0.9*	0.2*
Nunes	Psyllium	Normalization of evacuation	60	86.7%	30.0%
Lopez Roman	Inulin	Straining during defecation	32	35.7%	78.6%
Badiali	Bran	Straining during defecation	16	55.6%	28.6%

Soluble Fiber improved global symptoms 86% vs. 47% with placebo (n=4 studies)
The results of studies of insoluble fiber conflict (n=2 studies)
* Represents the number of bowel movements per week

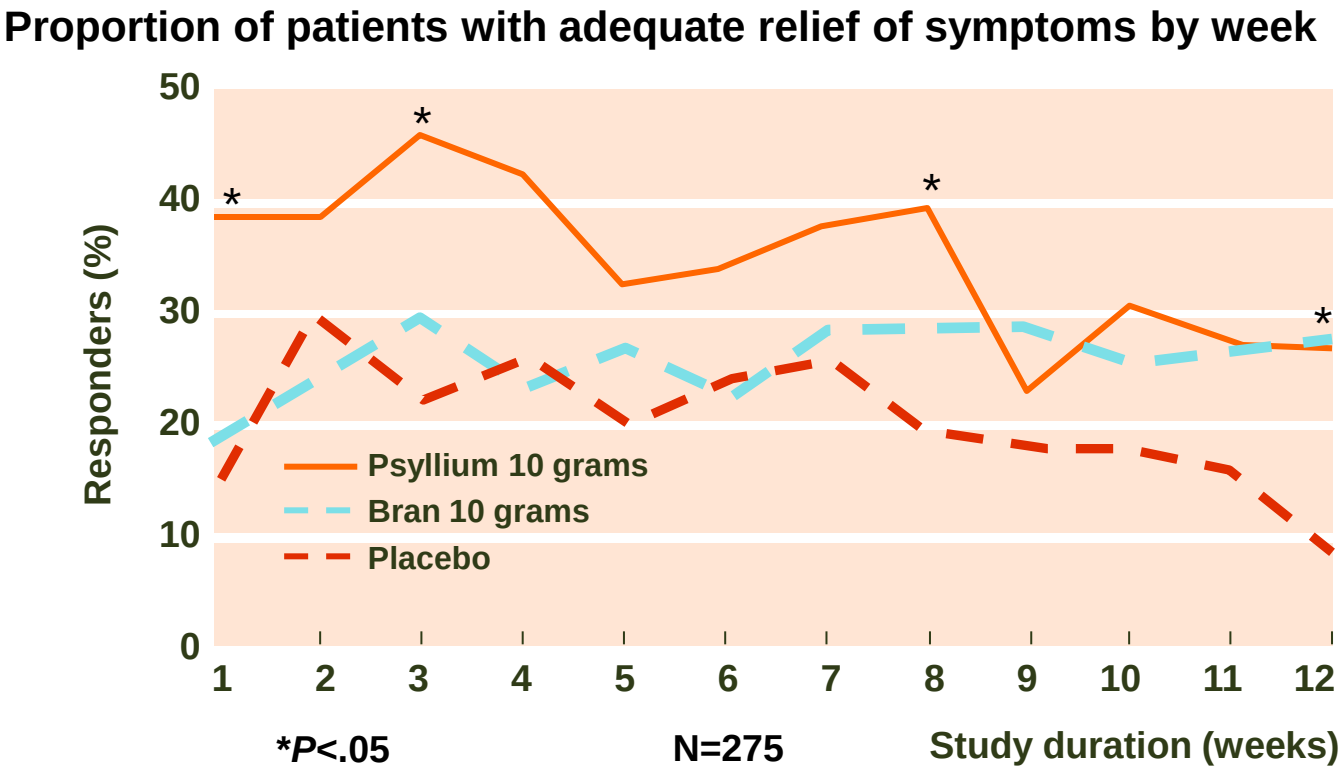
Suarez NC, Ford AC. *Aliment Pharmacol Ther.* 2011; 33: 895–901..

Fiber in IBS-C

- Most effective in improving constipation symptoms, not abdominal pain!
- Limited number of studies; small sample size; only 2 studies limited enrollment to IBS-C
  - Psyllium (ispaghula husk) (5 clinical trials)
    - Moderately effective (Grade 2C)
  - Wheat bran:
    - No more effective than placebo in relieving global symptoms of IBS
- Side effects: gas, bloating and discomfort

Brandt LJ et al. *Am J Gastroenterol* 2002;97 suppl:S7-26.
Ford AC et al. *BMJ*. 2008;337:a2313.

Soluble vs Insoluble Fiber for IBS



Responder: Adequate symptom relief

Bijkerk CJ et al. *BMJ*. 2009;339:b3154

Osmotic Laxatives

- Poorly or non-absorbed substances which result in secretion of water in the intestines. Generally take 1-2 days to work
  - Salts (e.g., magnesium and phosphate)
  - Disaccharides (e.g., lactulose)
  - Sugar alcohols (e.g., sorbitol or mannitol)
  - Polyethylene glycol (e.g. PEG-3350)
- Pts with renal or cardiac insufficiency may experience electrolyte /volume overload to Mg or Phosphorus absorption

Osmotic Laxatives in CC

Osmotic Laxative	Studies	Result
Lactulose	• 3 RDBPC • 2 well designed	• All trials lactulose > placebo • Lactulose improved stool consistency and # BM/day
Polyethylene Glycol (PEG)	• 3 RDBPC • All well designed • 2 compared PEG and lactulose	• PEG improved stool frequency and consistency, reduced straining • Overall effectiveness higher vs. lactulose
Sorbitol	• 1 RCT vs lactulose	• Efficacy in the elderly similar to lactulose
Magnesium	• No studies	

1. Brandt LJ, et al. *Am J Gastroenterol*. 2005;100:S5.

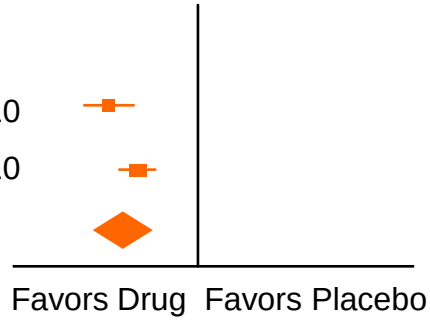
Stimulant Laxatives in CC

- Increase contractions of the bowel through effects on the nerves and/or muscles.
- Three major classes:
  - Senna, Bisacodyl, Cascara
- Two recent randomized trials with stimulants

1.1.2 Stimulant laxatives	Laxative		Placebo		Weight	Risk Ratio	
Kamm 2010	86	247	89	121	**22.2%**	0.47 [0.39, 0.58]	2010
Mueller-Lissner 2010	116	233	110	134	27.6%	0.61 [0.52, 0.71]	2010
Subtotal (95% CI)		**480**		**255**	**49.8%**	**0.54 [0.42, 0.69]**	
Total events	202		199				

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.80$, df = 1 (P = 0.05); $I^2 = 74\%$

Test for overall effect; Z = 4.92 ($p < 0.00001$)



Ford A C , Suares N C *Gut* 2011;60:209-218

Bisacodyl for Chronic Constipation

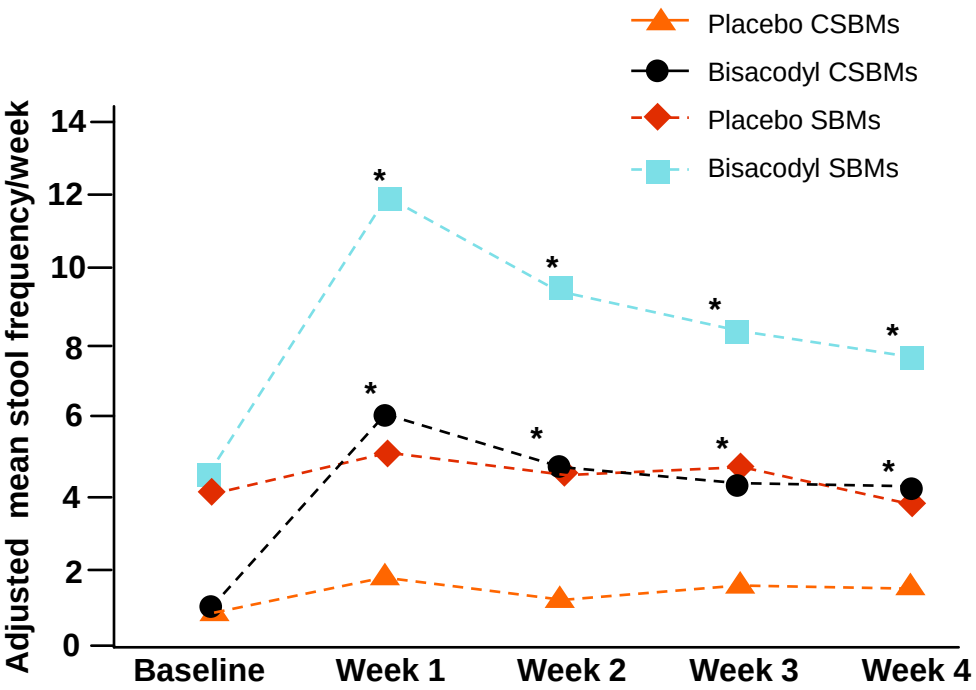
Rome III Functional Constipation

- Bisacodyl 10 mg (n=247)
- Placebo (n=121)

Dose titration down was allowed

<u>Adverse Events</u>

- Diarrhea = 53%
- Abdominal pain = 25%
- AE leading to discontinuation = 18%



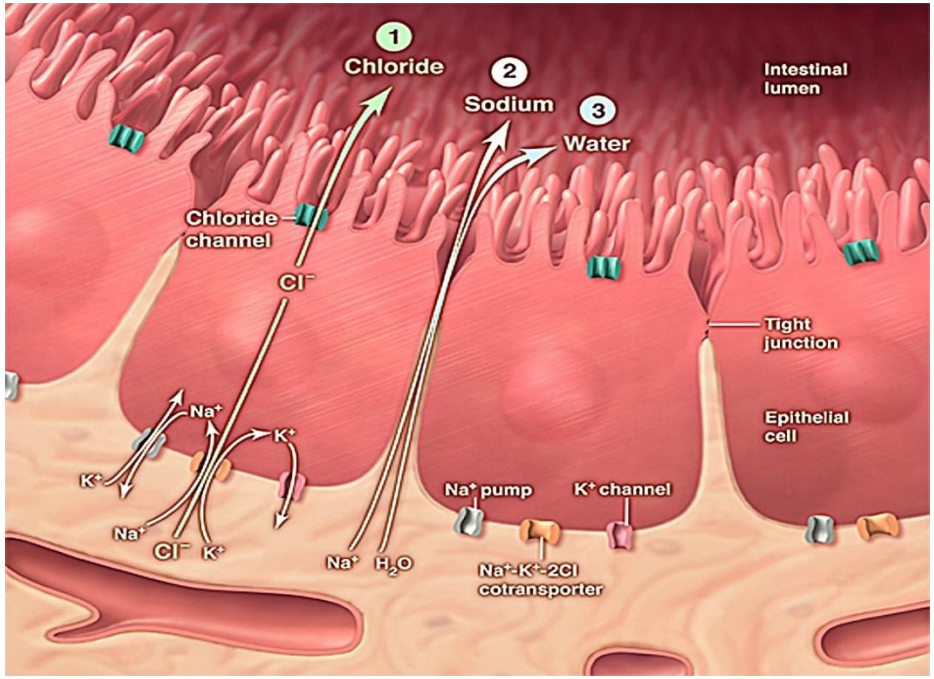
Laxatives in IBS-C

- No well conducted randomized controlled trials in adults with IBS-C
- One study in adolescents with PEG (n=27)

Koshoo V, *Alimentary Pharmacology Therapeutics* 2006; 23:191-196

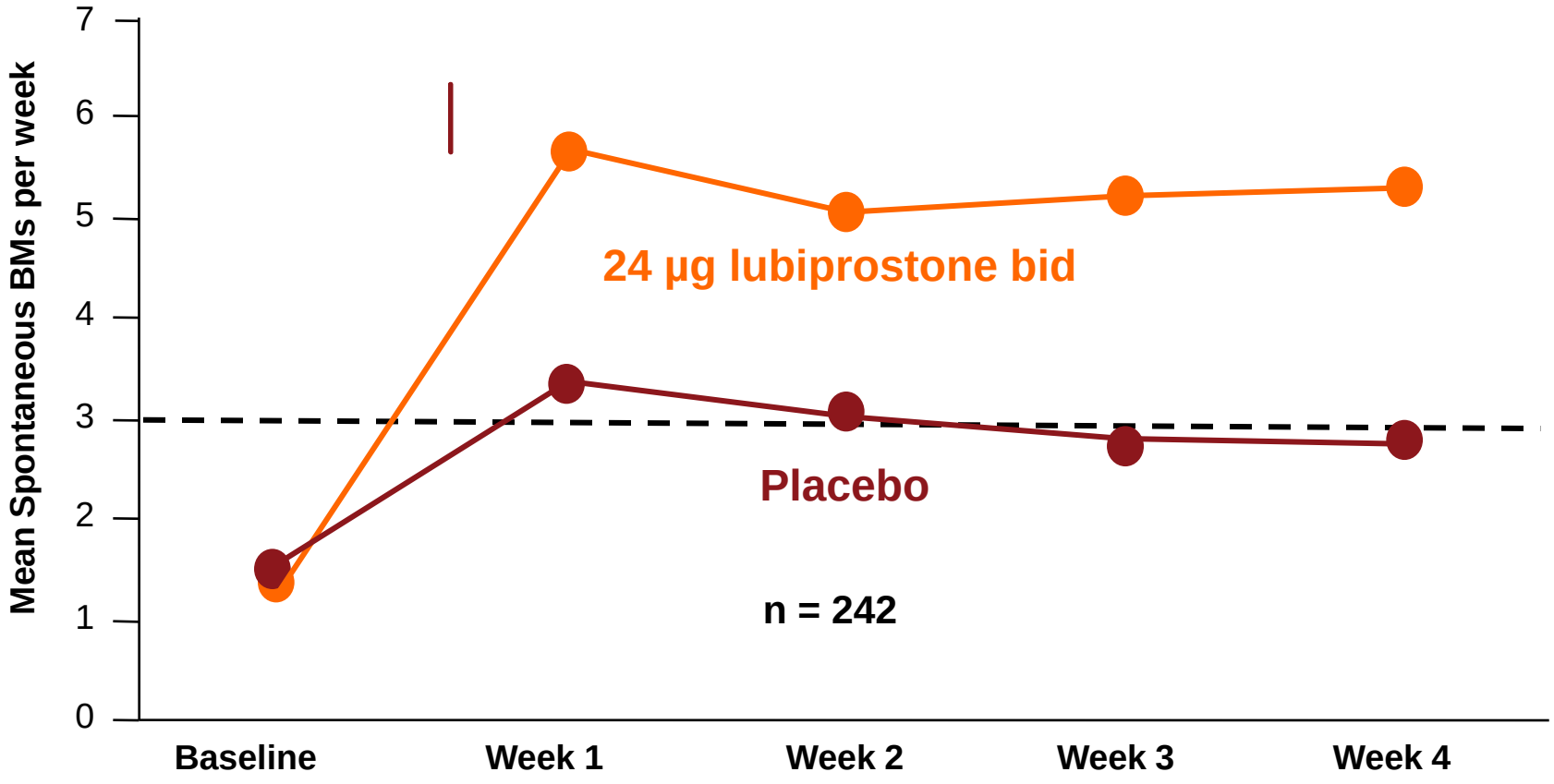
Lubiprostone: Chloride Channel Activator

- Locally-acting GI-targeted bicyclic functional fatty acid
- Selectively activates ClC-2 channels, enhancing intestinal fluid secretion
- Accelerates small bowel and colonic transit



Cuppoletti J et al. *Am J Physiol Cell Physiol*. 2004;287:C1173-1183;
Camilleri M et al. *Am J Physiol Gastrointest Liver Physiol*. 2006;290:G942-947.

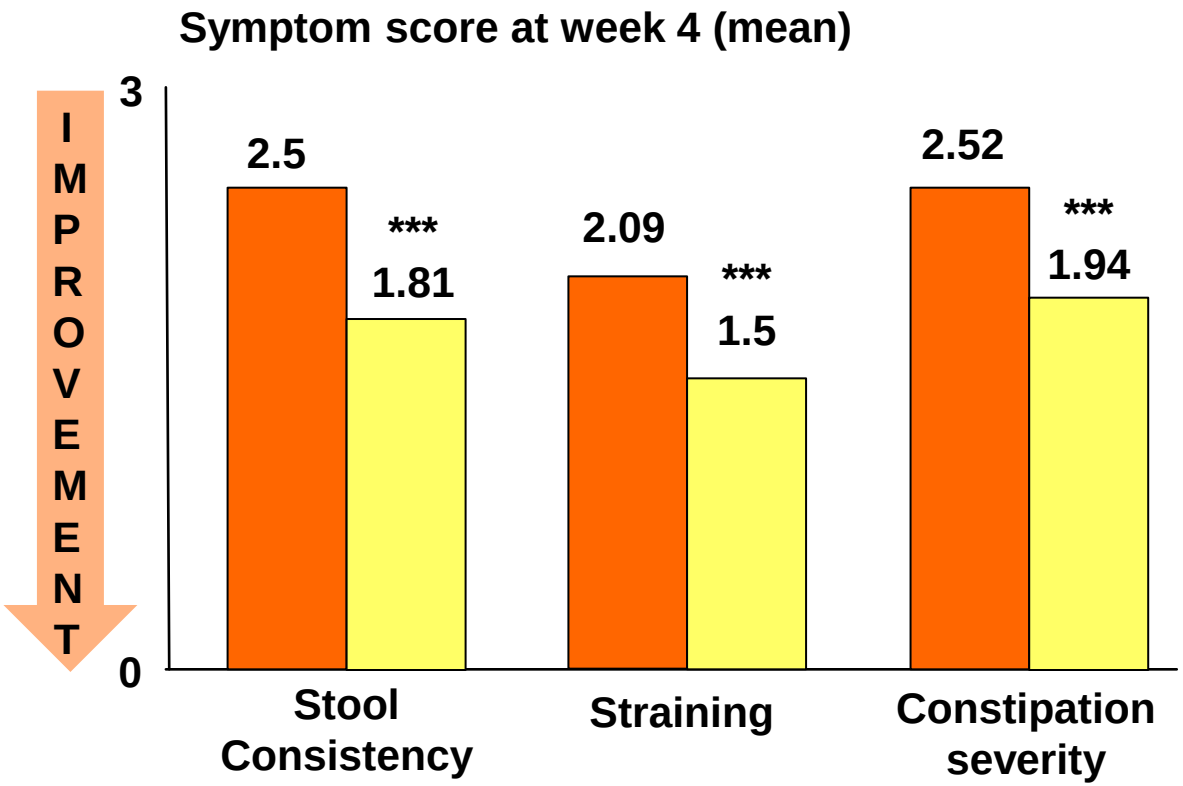
Effects of Lubiprostone on Number of Spontaneous Bowel Movements in CC



Adverse Events: Nausea (31%) Diarrhea (13%) and Headaches (13%)

Johanson JF et al. *Am J Gastroenterol*. 2008;103:170.

Treatment of Chronic Constipation: Lubiprostone



Placebo (n=122)
Lubiprostone 24 mcg bid (n=120)

Straining:
0=absent
1=mild
2=moderate
3=severe
4=very severe

Consistency:
0=very loose
1=loose
2=normal
3=hard
4=very hard

***** p≤0.0003 vs placebo**

- Stool consistency, straining and constipation severity improved significantly with lubiprostone *vs* placebo throughout the 4 week period

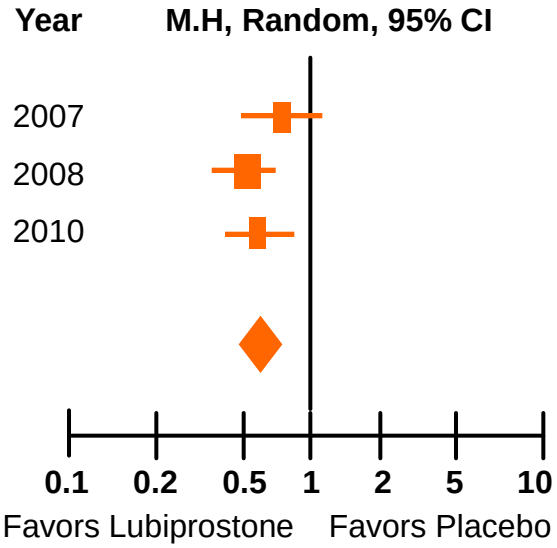
Johanson JF et al. *Am J Gastroenterol*. 2008;103:170.

Forest Plot of Randomised Controlled Trials of Lubiprostone Versus Placebo in Chronic Constipation

Study or Subgroup	Events	Total	Events	Total	Weight	M.H, Random, 95% CI	Year
Johanson 2007	52	96	22	33	27.2%	0.81 [0.60, 1.10]	2007
Johanson 2008	51	120	90	124	39.1%	0.59 [0.46, 0.74]	2008
Barish 2010	48	119	72	118	33.7%	0.66 [0.51, 0.86]	2010
Total (95% CI)		**335**		**275**	**100.0%**	**0.67 [0.56, 0.80]**	
Total events	151		184				

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.84$, df = 2(P = 0.24); $I^2 = 30\%$

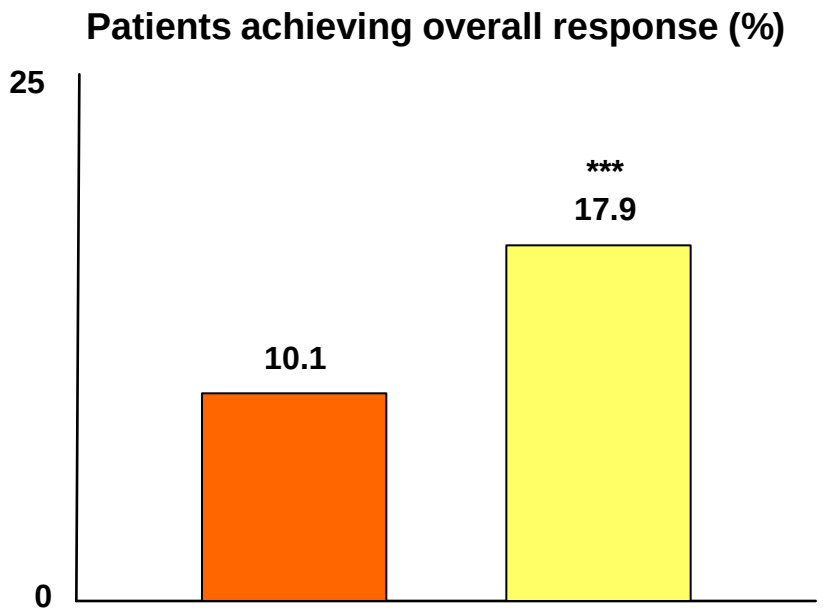
Test for overall effect: Z = 4.37 (P < 0.0001)



Ford A C , Suares N C *Gut* 2011;60:209-218

Lubiprostone for IBS-C

- Pooled data from 2 Phase III studies



Placebo (n=387)

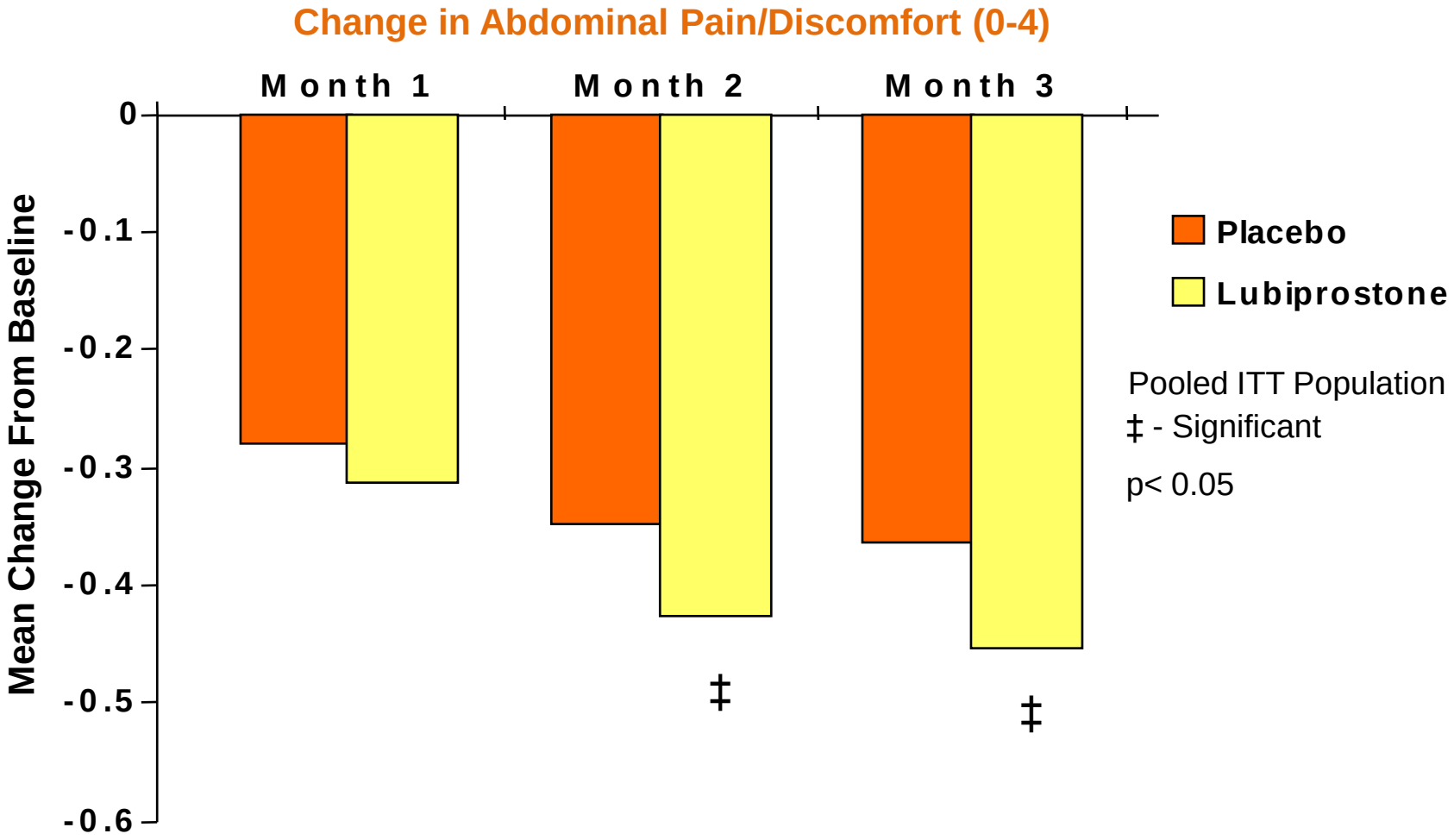
Lubiprostone 8 mcg bid (n=780)

Overall responder = monthly responder for ≥2 of 3 months
Monthly responder = at least moderate relief 4 out of 4 weeks or significant relief 2 out of 4 weeks

*** p=0.001 vs placebo

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

Lubiprostone: IBS with Constipation



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

Lubiprostone in IBS-C: Adverse Events

	Placebo N=387	**Lubiprostone 8 mcg BID** N=779
Serious Adverse Events	1%	1%
Treatment-related Adverse Events	21%	22%
Nausea	4%	8%
Diarrhea	4%	6%
Abdominal Pain	5%	4%
Cardiovascular-related Events (Mild tachycardia reported in 1 patient)	0%	<1%
Discontinuation due to adverse events	6%	5%

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

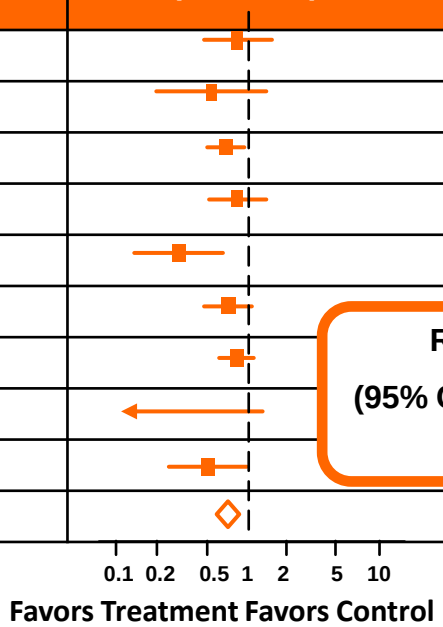
Antidepressants in IBS

- Reduce abdominal pain/discomfort
- Studies generally include all subtypes of IBS
  - Tricyclic antidepressants
    - anti-cholinergic effects
  - SSRIs
    - increase serotonin in the GI tract

Tricylic Antidepressants in IBS

- Tricyclic Antidepressants
  - reduces pain/global sxs
  - target dose (50 mg/day)
  - AEs are common

Study (Year, Drug, Dose)	Treatment n/N	Control n/N	RR (Random) 95% CI
Heefner (1978, desipramine 150 mg daily)	10/22	12/22	
Myren (1982, trimipramine 50 mg daily)	5/30	10/31	
Nigam (1984, amitriptyline 12.5 mg daily)	14/21	21/21	
Boerner (1988, doxepin 50 mg daily)	16/42	19/41	
Bergmann (1991, trimipramine 50 mg daily)	5/19	14/16	
Vij (1991, doxepin 75 mg daily)	14/25	20/25	
Drossman (2003, desipramine 50-150 mg daily)	60/115	36/57	
Talley (2008, imipramine 50 mg daily)	0/18	5/16	
Vahedi (2008, amitriptyline 10 mg daily)	8/27	16/27	
Subtotal (95% CI)	**319**	**256**	

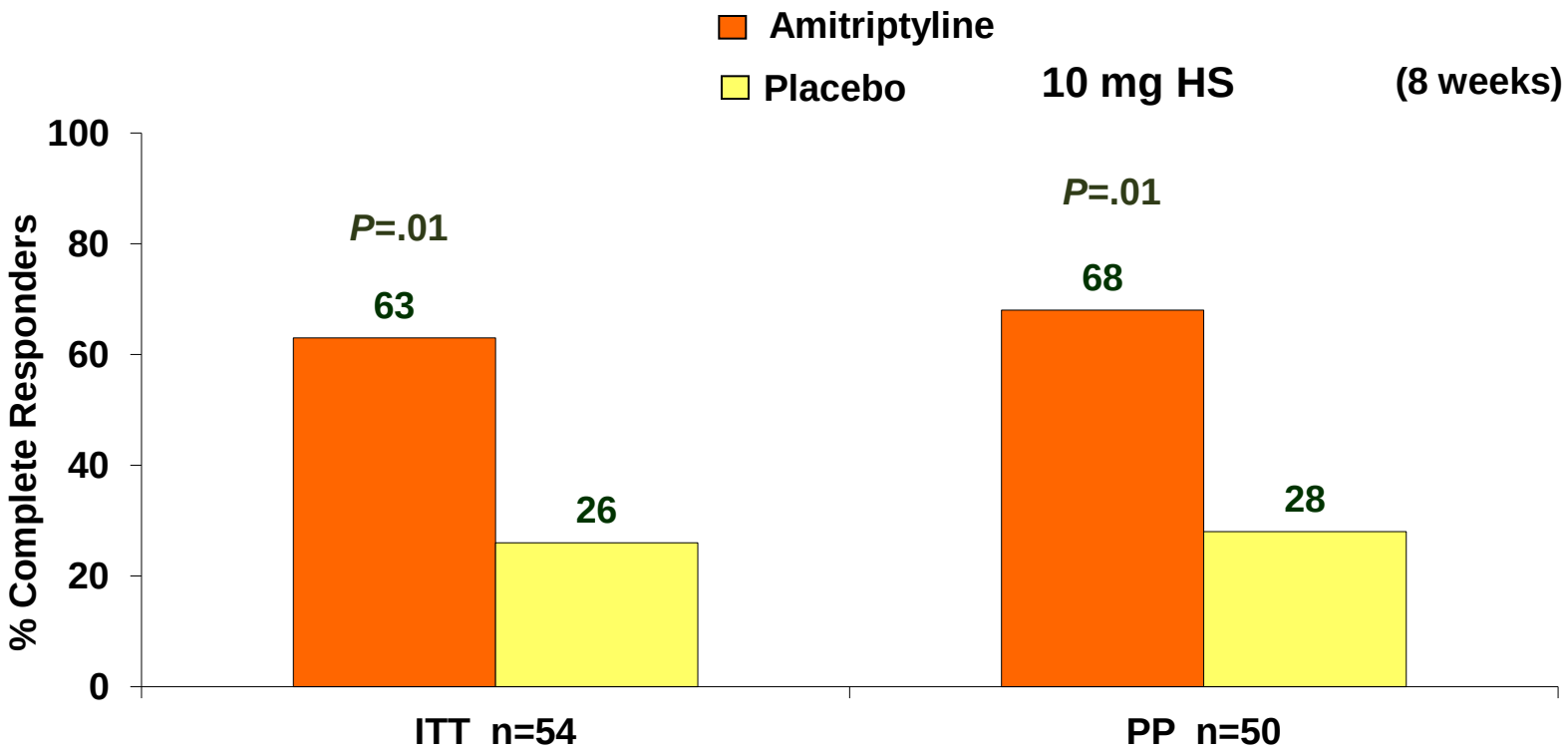


RR=0.68

(95% CI=0.56-0.83)

NNT=4

Low-dose Amitriptyline vs Placebo for IBS-D

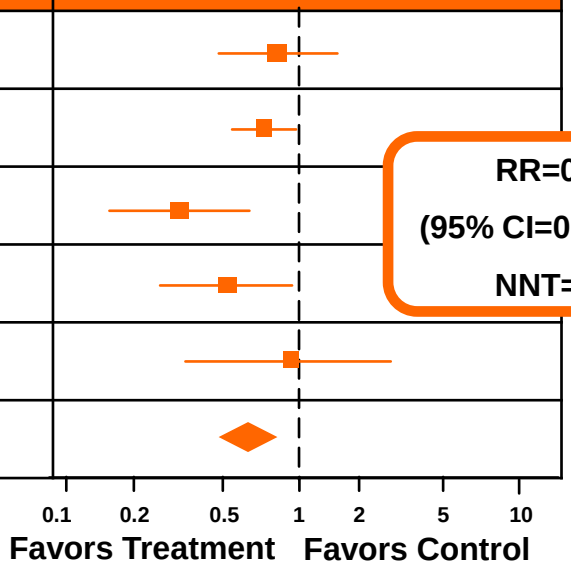


No significant difference in AEs between groups

Vahedi H et al. *Aliment Pharmacol Ther*. 2008;27:678-84.

SSRIs in IBS

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

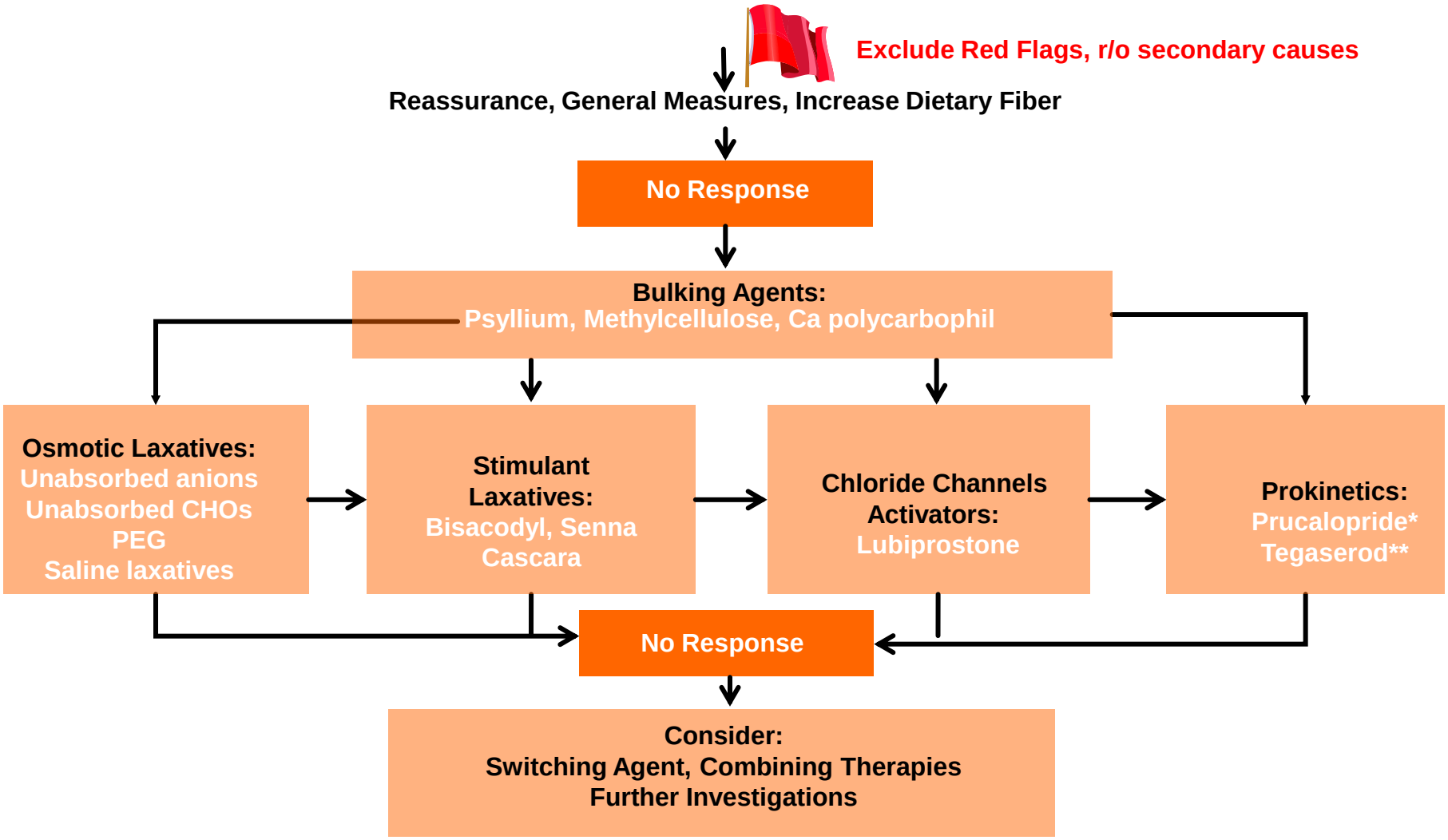


RR=0.62
(95% CI=0.45-0.87)
NNT=3.5

- Most patients note improvement in overall well-being
  - no studies show any benefit regarding bowel habits
  - abdominal pain generally not improved

ACG IBS Task Force. *Am J Gastroenterol.* 2009;104 (S1):S1-S35.

Chronic Constipation

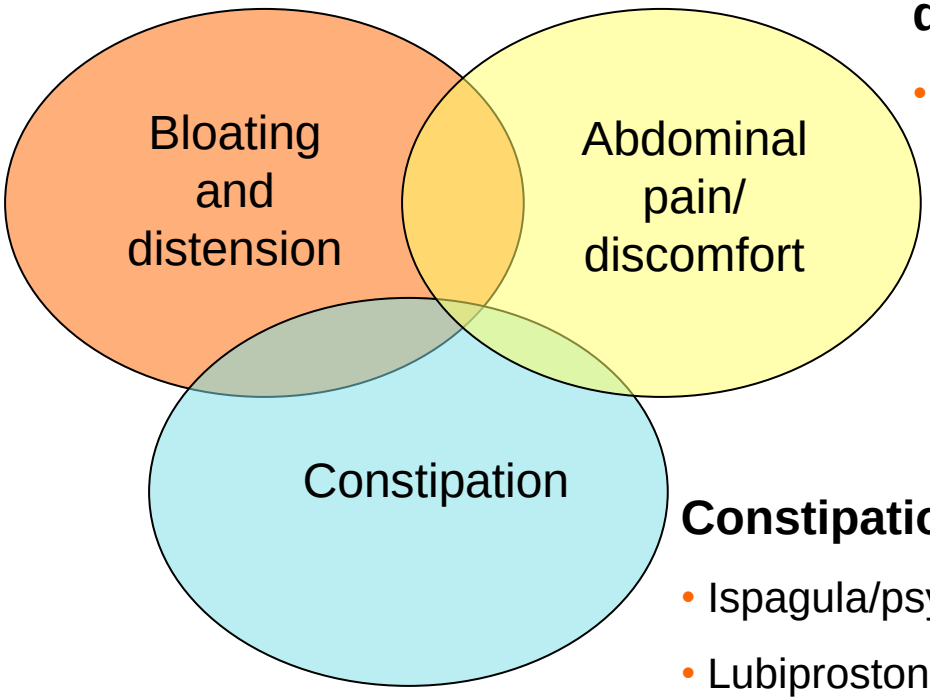


*Not available in the U.S.
**Available through the FDA with an IND

Pharmacologic Management of IBS

Bloating

- Probiotics
- Antibiotics



Abdominal pain/ discomfort

- Antidepressants

Constipation

- Ispagula/psyllium
- Lubiprostone
- Osmotic laxatives

Brandt LJ et al. *Am J Gastroenterol*. 2009;104 Suppl 1:S1-35;
Brandt LJ et al. *Am J Gastroenterol*. 2002;97:S7-26;
Drossman DA et al. *Gastroenterology*. 2002;123:2108-2131.

Conclusions

- There remains a need to safe and effective therapies in both CC and IBS-C
- Improving bowel function is performed with fiber, laxatives and lubiprostone
- IBS-C treatment is generally aimed at the predominant symptom