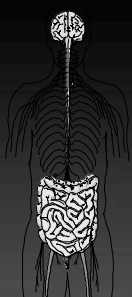


## Irritable Bowel Syndrome and Chronic Constipation

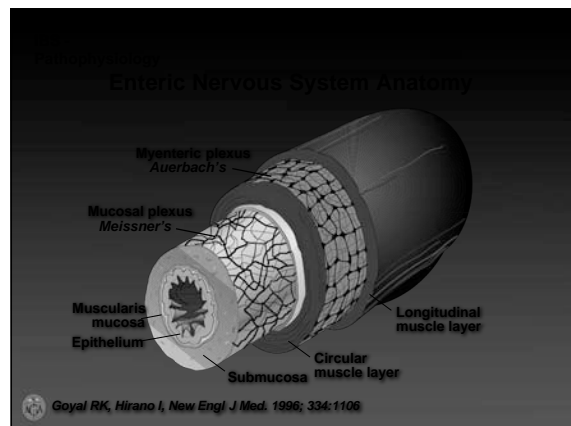
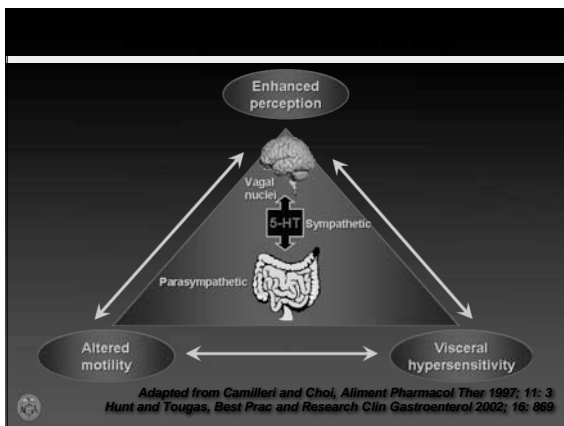
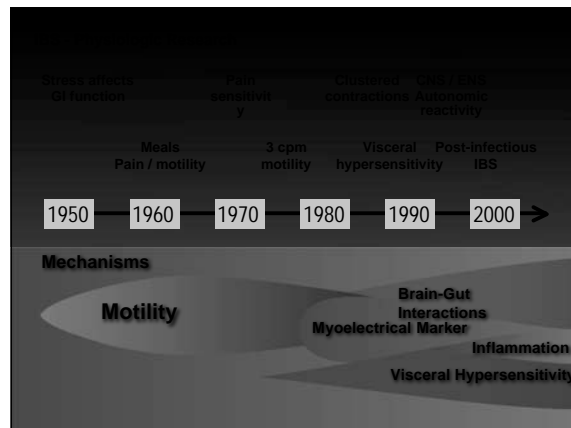
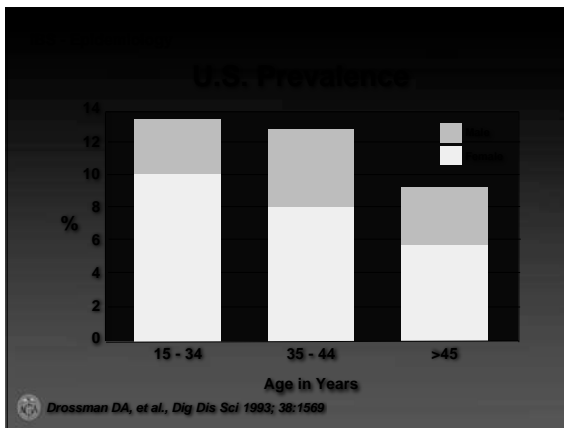


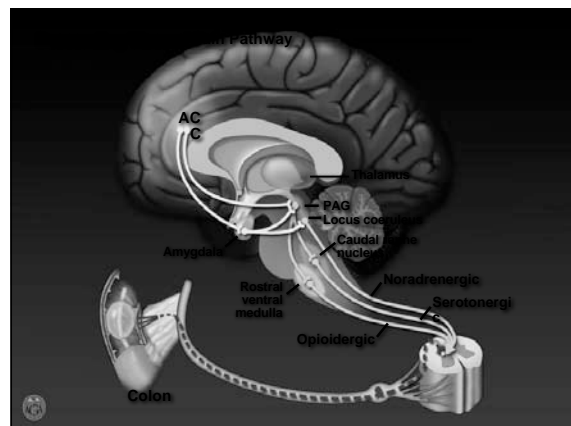
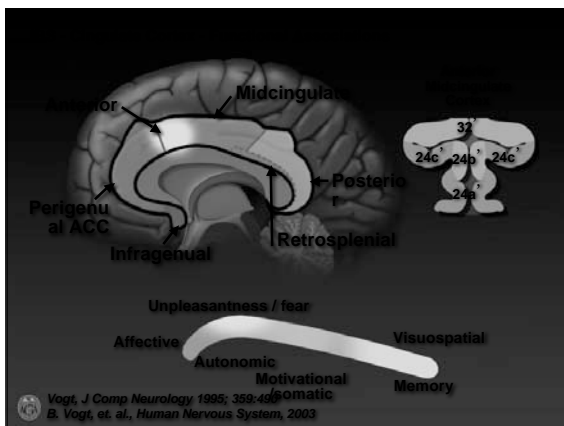
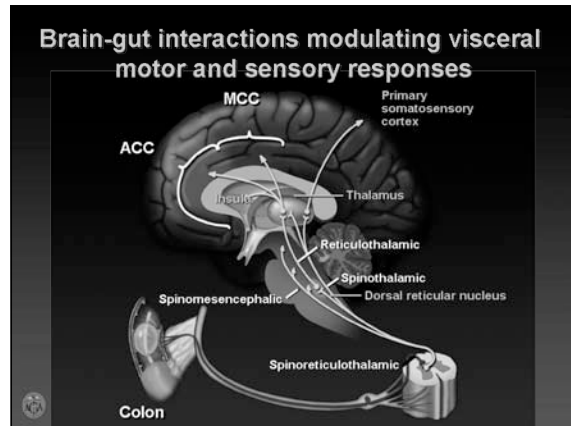
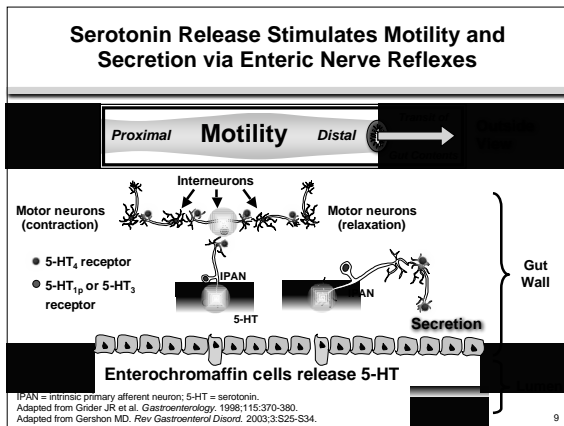
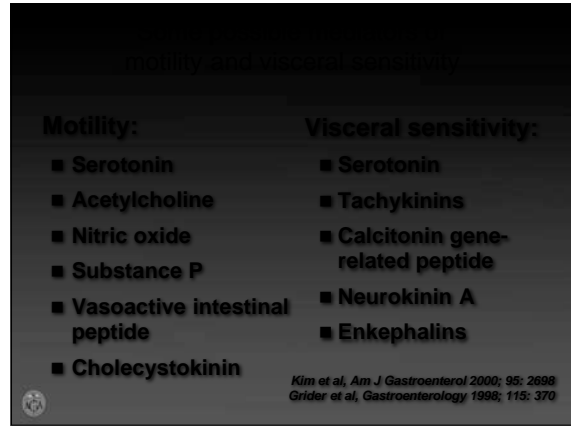
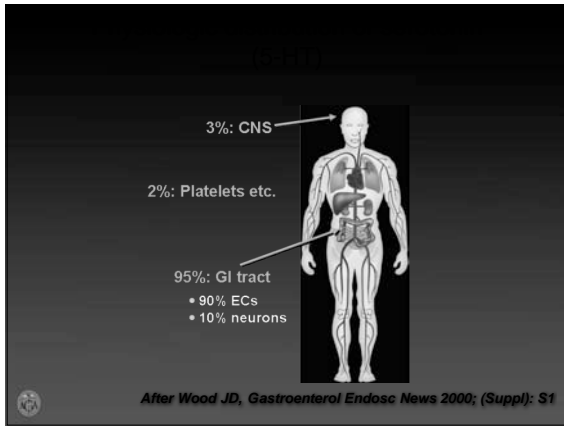
**Susan Lucak, M.D.**  
Columbia University Medical Center

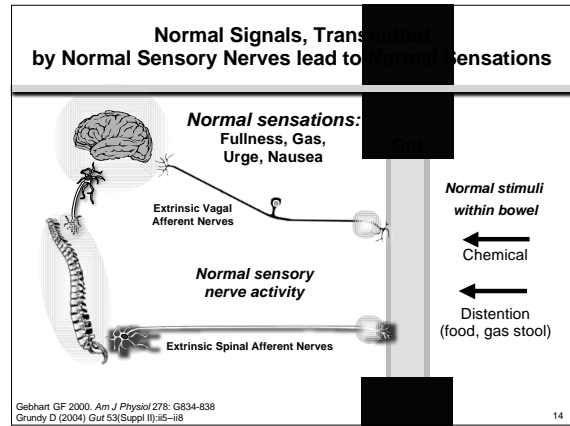
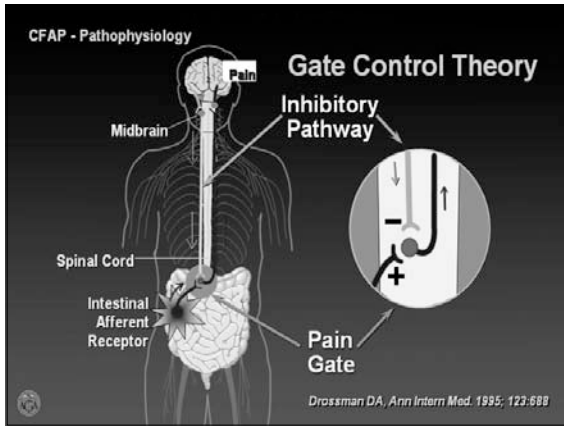
### What is IBS?

- a chronic, intermittent gastrointestinal condition
- a functional bowel disorder without evidence of structural or biochemical abnormalities
- characterized by **ABDOMINAL PAIN** or **DISCOMFORT** associated with altered bowel function:
  - diarrhea
  - constipation
  - bloating or feeling of distension
  - passage of mucus

*Drossman et al, Gastroenterology 1997; 112: 2120*







### IBS: ROME III

- Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with 2 or more:
  - Improvement with defecation
  - Onset associated with a change in frequency of stool
  - Onset associated with a change in form (appearance) of stool

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

Longstreth et al, *Gastroenterology* 2006; 130:1480

### ROME III bowel habit sub-classification

- IBS-C:** >25% hard or lumpy stools and <25% loose or watery stools
- IBS-D** >25% loose or watery stools and <25% hard or lumpy stools
- IBS-M** >25% loose or watery stools and >25% hard or lumpy stools
- IBS-U** Insufficient abnormality of stool consistency to meet criteria for IBS-C, IBS-D, or IBS-M

Longstreth et al, *Gastroenterology* 2006; 130:1480

### IBS subgroups

- Proportions of patients in each subgroup stable over time but:
  - 75% will experience a change in subgroup over time
  - IBS-M least stable – more likely to transition to IBS-C than IBS-D
  - transitions from IBS-C to IBS-D in less than a third of patients over a year

Simren, *Scand J Gastroenterol* 2001; 36: 545  
Tillich et al, *Am J Gastroenterol* 2005; 100: 896  
Mearin et al, *Eur J Gastroenterol Hepatol* 2003; 15: 165  
Drossman et al, *Gastroenterology* 2005; 128: 589

### 2002 Treatment of IBS

Abdominal pain / discomfort

- Antispasmodics
- Antidepressants
  - TCA's / SSRIs
- Alosetron
- Tegaserod

**Abdominal pain / discomfort**

**Bloating / distention**

- Tegaserod
- Dietary changes
- ? Probiotics
- ? Antibiotics

**Altered bowel function**

Constipation

- Fiber
- MOM/PEG solution
- Tegaserod

Diarrhea

- Loperamide
- Other opioids
- Alosetron

Brandt, *Am J Gastroenterol* 2002; 97: S7  
Drossman, *Gastroenterology* 2002; 123: 2108

### 2000 5-HT<sub>3</sub> Antagonist: Mechanisms of Action

Kim D-Y, Camilleri M. *Am J Gastroenterol.* 2000;95:2698-2709.

5-HT<sub>3</sub> receptor on vagal or spinal afferent

### 5-HT<sub>3</sub> receptor antagonists

- Delay small bowel and colonic transit<sup>1,2</sup>
  - treat diarrhea
- Increase colonic compliance<sup>1</sup>
  - improve fecal urgency
- Inhibit chloride secretion<sup>1</sup>
  - make stools more formed
- Blunt the gastrocolonic response<sup>1</sup>
  - improve urgency
- Affect visceral afferent<sup>1</sup>
  - diminish abdominal pain

1. Kim D-Y, Camilleri M. *Am J Gastroenterol.* 2000;95:2698-2709.  
2. Viramontes BE et al. *Am J Gastroenterol.* 2001;96:2671-2676.

### 2002

Tegaserod

Serotonin (5-HT)

- Tegaserod is a 5-HT<sub>4</sub> receptor agonist
- new class of compound: aminoguanidine indoles
- Structure similar to serotonin

Camilleri, *Alliment Pharmacol Ther* 2001; 15: 277

### Impaired 5HT-Release Leads to Impaired Enteric Reflexes, Dysmotility, and Reduced Secretion

Proximal **Dysmotility** Distal

Motor neurons (contraction) Interneurons Motor neurons (relaxation)

5-HT<sub>4</sub> receptor  
5-HT<sub>1A</sub> or 5-HT<sub>3</sub> receptor

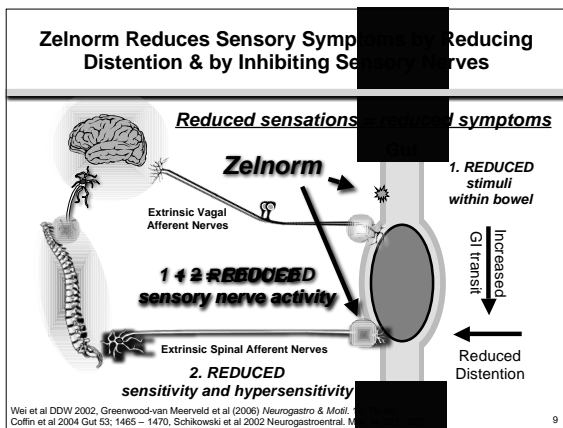
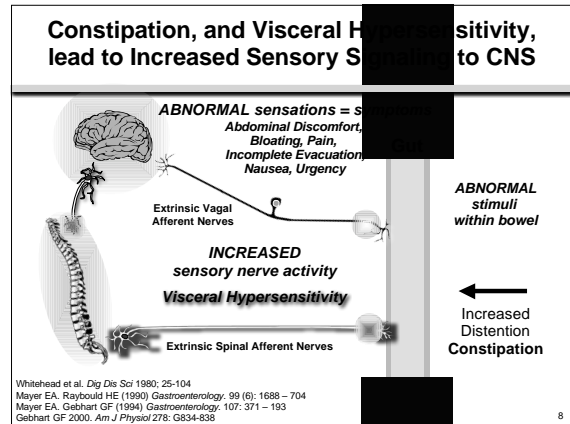
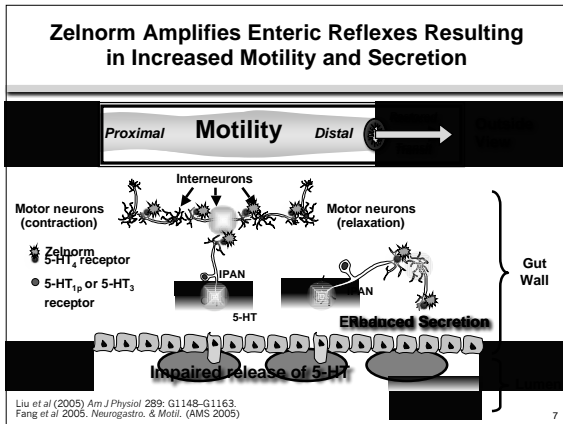
5-HT

Reduced Secretion

Impaired release of 5-HT

Gut Wall

Dunlop et al (2005) *Clin Gastro. & Hepatol.* 3, 349-357  
Atkinson et al (2006) *Gastroenterology* 130; 34-43.

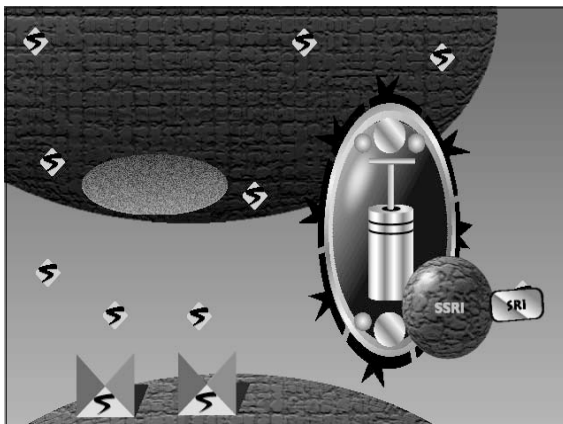


### Effect of tegaserod on additional dysmotility symptoms of IBS-C<sup>1</sup>

- ↑ Improved stool consistency
- ↑ Increased number of BMs/wk
- ↓ Reduced straining
- ↓ Relieved bloating
- ↓ Reduced abdominal pain / discomfort

■ In a double-blind RCT (tegaserod n=1645; placebo n=405): IBS-C QoL was significantly better in patients treated with tegaserod, p=0.005 vs placebo<sup>2</sup>  
■ Efficacy beyond 12 weeks has not been studied  
■ Response rates vs placebo were greater at month 1 than at month 3

<sup>1</sup>Kellow et al, *Gut* 2003; 52: 671  
<sup>2</sup>Patrick et al, *Gastroenterol* 2005; 128: A287



- Single protein
- Mediates reuptake of 5-HT from the synaptic cleft
- SERT in the **gut** is similar to SERT in the **brain** of the same species
- neurons (ENS) and crypt epithelial cells synthesize SERT proteins
- Function of the SERT: to control the concentration + actions of 5-HT in the gut and limit desensitization of 5-HT receptors

Chen J-X, Pan H, Rothman TP, et al. *Am J Physiol* 1998; 275:G433-8  
Wade PR, Chen J, Jaffe B et al. *J Neurosci* 1996; 16:2352-64

Sertraline (Zoloft) 50-250 mg  
 Fluoxetine (Prozac) 20-80 mg  
 Fluvoxamine (Luvox) 100-300 mg

### Therapeutic effects of fluoxetine in IBS-C patients: A randomized-controlled study

Treatment period was 12 weeks

■ At week 4, all symptoms evaluated (bloating, discomfort, stool consistency, change in bowel habit <3 bowel movements / week) less frequent in the fluoxetine patients vs placebo (p<0.05)  
 ■ Mean number symptoms per patient decreased from 4.6-0.7 in fluoxetine patients vs 4.5-2.9 in control patients (p<0.001)  
 ■ Low dose fluoxetine effective in IBS-C patients, but there is need for further studies  
*Vahedi et al, Aliment Pharmacol Ther 2005; 22: 381*

### Efficacy of rifaximin for chronic bloating and flatulence in IBS patients

■ Antibiotic  
 ■ Modest effect in short term management of gas-related abdominal symptoms  
 ■ Study limitations: short duration of treatment and follow-up, small sample size  
*Sharara et al, Am J Gastroenterol 2006; 101: 326*

# CHRONIC CONSTIPATION IDIOPATHIC

### Prevalence and incidence of constipation in the US

■ Prevalence:  
 • estimated 55 million Americans (prevalence 28%)<sup>1</sup>  
 > men 12%<sup>2</sup>  
 > women 16%<sup>2</sup>  
 > elderly individuals 40%<sup>3</sup>  
 ■ Onset rate 40 / 1000 person-years<sup>4</sup>

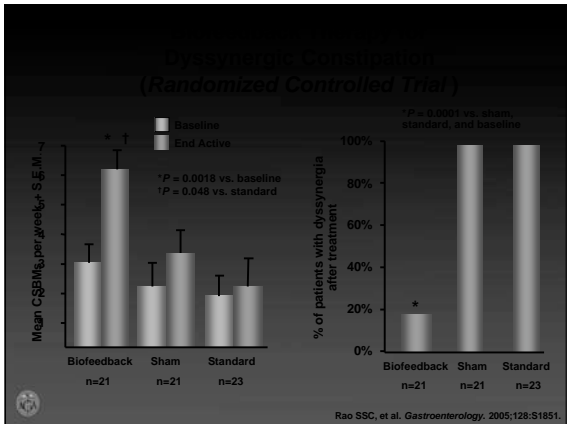
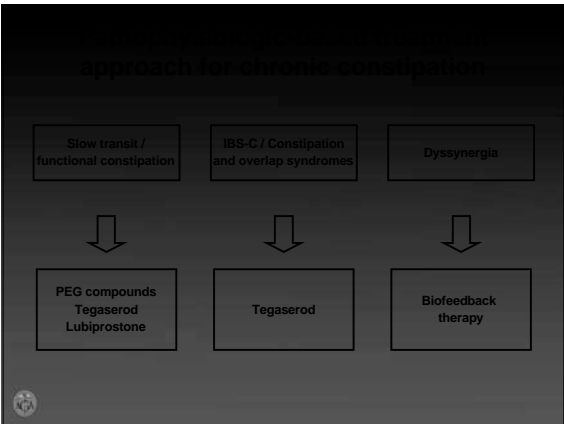
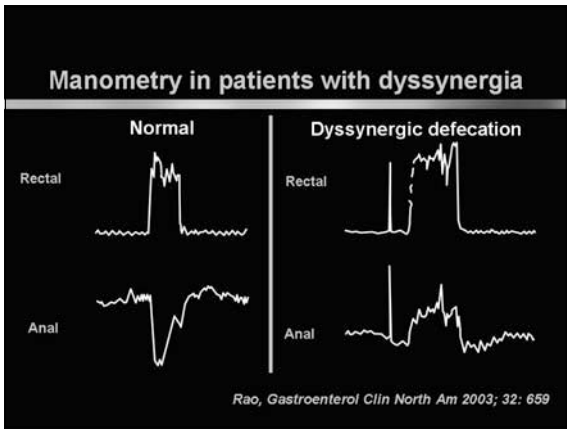
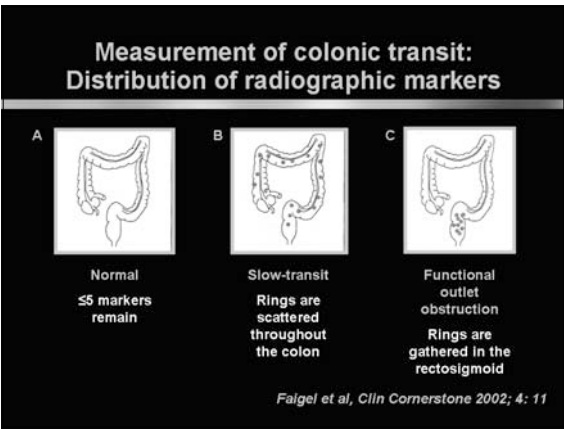
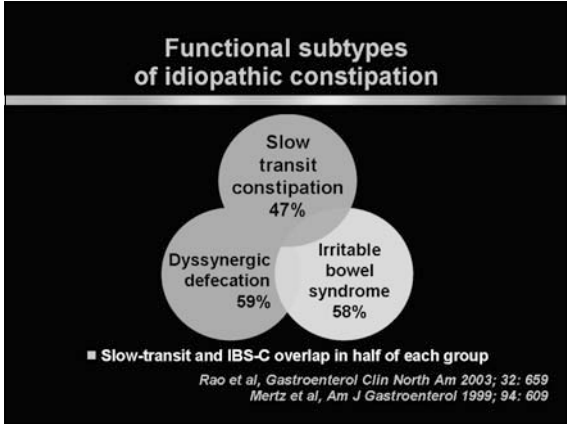
<sup>1</sup>Locke et al, *Gastroenterology* 2000; 119: 1766  
<sup>2</sup>Stewart et al, *Am J Gastroenterol* 1999; 94(12): 3530  
<sup>3</sup>Talley et al, *Am J Gastroenterol* 1996; 91: 19  
<sup>4</sup>Talley et al, *Am J Epidemiol* 1992; 136: 165

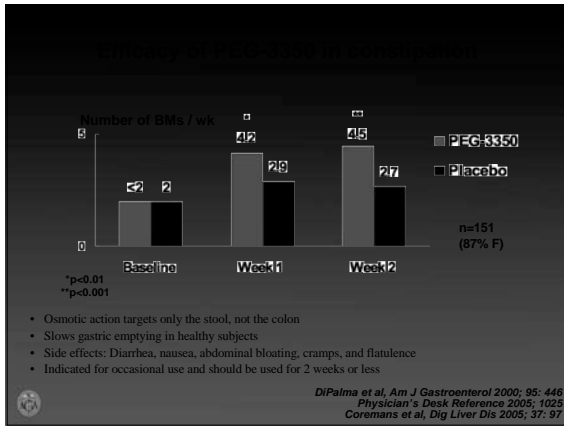
### Chronic Constipation and IBS-C Share GI Dysmotility Symptoms

Symptoms >3 months	Chronic Constipation	IBS-C
Straining	+++	+++
Hard/lumpy stools	+++	+++
<3 BM/wk	+++	+++
Feeling of incomplete evacuation	+++	+++
Bloating/abdominal distension	++	+++
Abdominal pain/discomfort	+	+++

CC and IBS-C lie along a spectrum of abdominal discomfort and pain

IBS-C = irritable bowel syndrome with constipation.  
 Thompson WG et al. *Gut*. 1999;45(suppl 2):II43-II47.  
 Drossman DA et al. *Gastroenterology*. 1997;112:2120-2137.



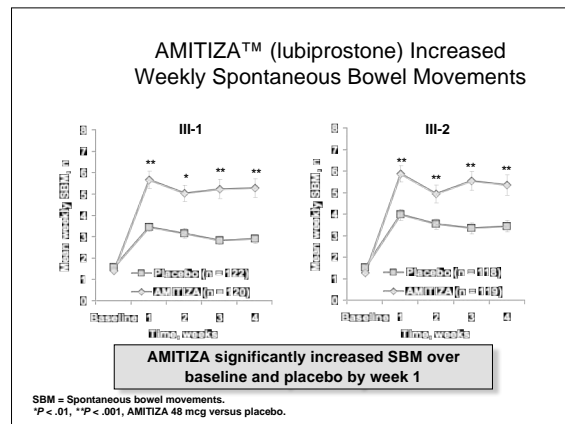
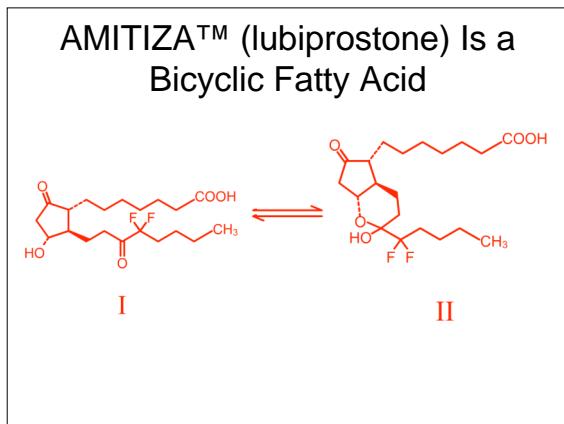
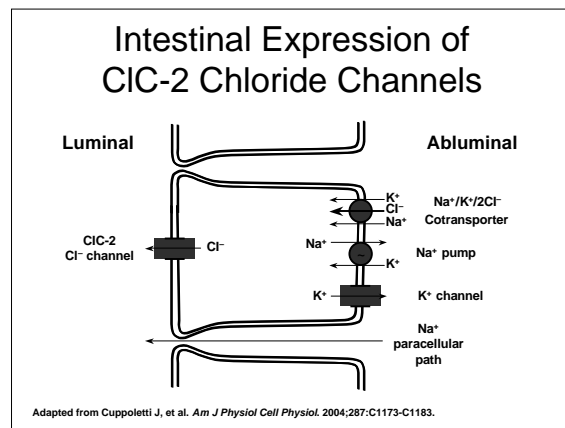
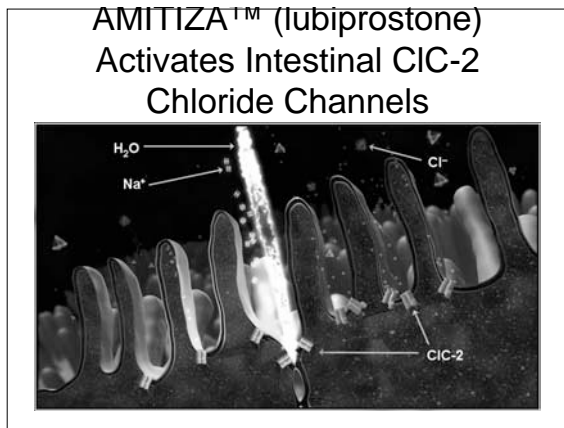


### Summary: Tegaserod in chronic constipation

**In chronic constipation, tegaserod:**

- Normalizes impaired motility and stimulates intestinal secretion
- Increases bowel movements
- Provides effective and sustained relief of:
  - straining
  - hard / lumpy stools
- Improves global constipation relief score
- Has a favorable safety profile

*Johanson et al, Gastroenterology 2003; 124(suppl. 1): A47*  
*Talley et al, Am J Gastroenterol 2003; 98(9): S269*





## AMITIZA™ (lubiprostone) Activates CIC-2 Chloride Channels

- Specific chloride channel-2 (CIC-2) activator
- Promotes fluid secretion
- Enhances intestinal fluid secretion to facilitate increased motility

Ueno R, et al. *Gastroenterology*. 2004;126(suppl 2):A298. Abstract M1109.

## Comparison of lubiprostone and tegaserod in CC

	Lubiprostone <sup>1</sup>	Tegaserod <sup>2</sup>
Description	Chloride channel activator	5-HT <sub>4</sub> agonist
Mechanism of action	Increases intestinal fluid secretion	Stimulates the peristaltic reflex Stimulates intestinal secretion Inhibits visceral sensitivity
Indications	CC in male and female patients	CC in male and female patients <65 years, IBS-C in female
Administration	Twice daily orally with food	Twice daily orally before meals
Patients experiencing SBM in first 24 hours <sup>3,4†</sup>	Lubiprostone 61.3%	Tegaserod 62%
Adverse Events in CC*	Diarrhea (13%) Headache (13.2%) Abdominal pain (6.7%) Nausea (31.1%)	Diarrhea (7%) Headache (15%)** Abdominal pain (5%) Nausea (5%)

<sup>†</sup>Different endpoints make the trials difficult to compare

\*AE rates for tegaserod in IBS-C are not listed here

\*\*Rate reported in IBS-C, only aggravated headache listed for CC (1%)

<sup>1</sup>Lubiprostone PI

<sup>2</sup>Tegaserod PI

<sup>3</sup>Johanson, *Am J Gastroenterol* 2005; 100: S324

<sup>4</sup>Kamm, *Am J Gastroenterol* 2005; 100: 362

## FDA-approved prescription medications for constipation

