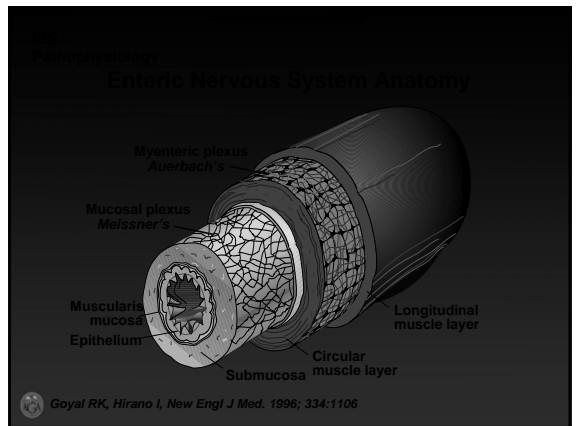
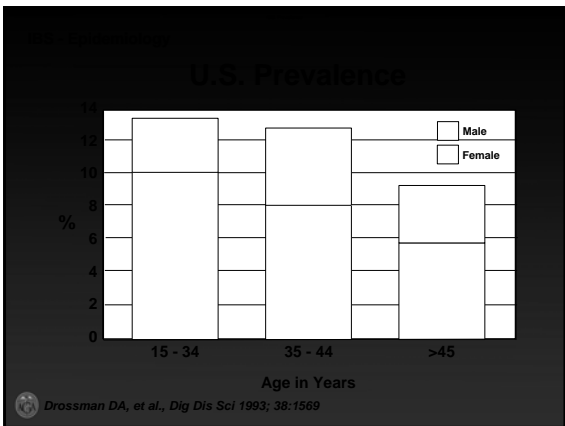
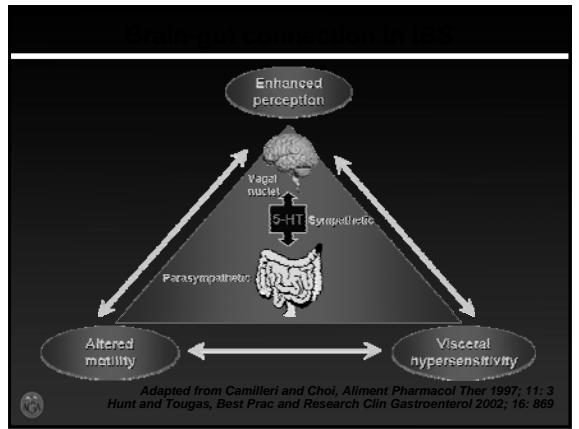
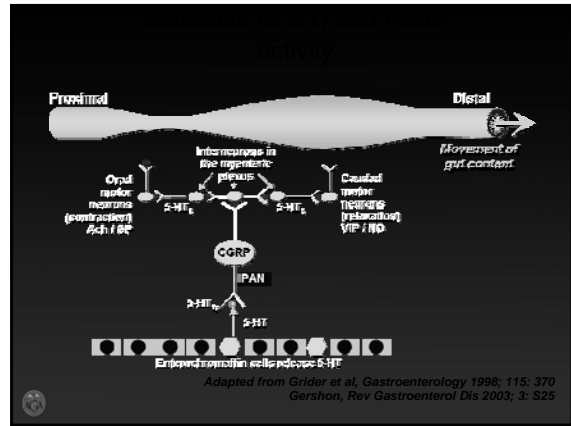
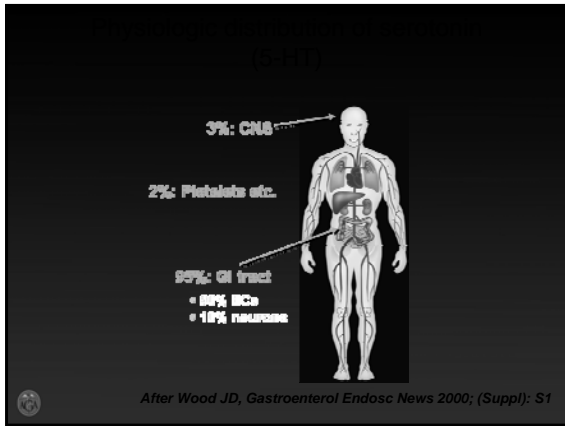


What is IBS?

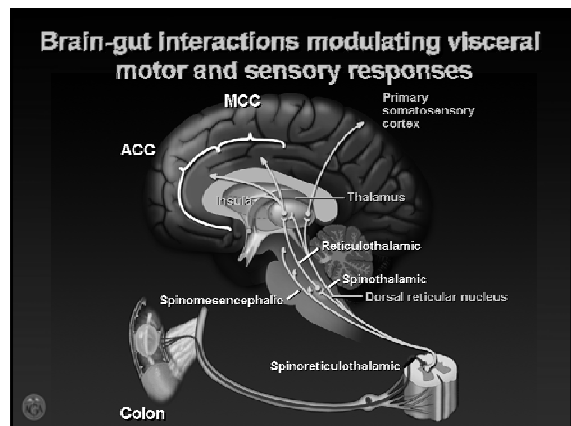
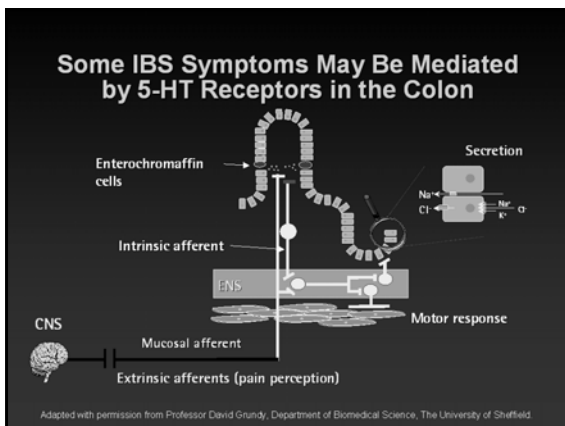
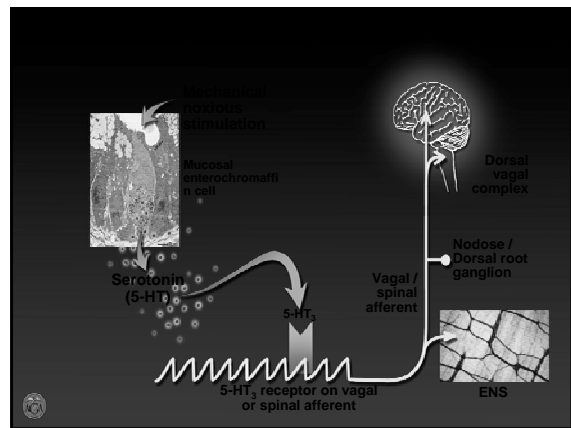
- a chronic, intermittent gastrointestinal condition
- a functional bowel disorder without evidence of structural or biochemical abnormalities
- characterized by abdominal pain or discomfort associated with altered bowel function:
 - diarrhea: >3BMs/day, loose stools, urgency
 - constipation: <3BMs/wk, hard/lumpy stools, straining
 - bloating or feeling of distension
 - sense of incomplete evacuation
 - passage of mucus

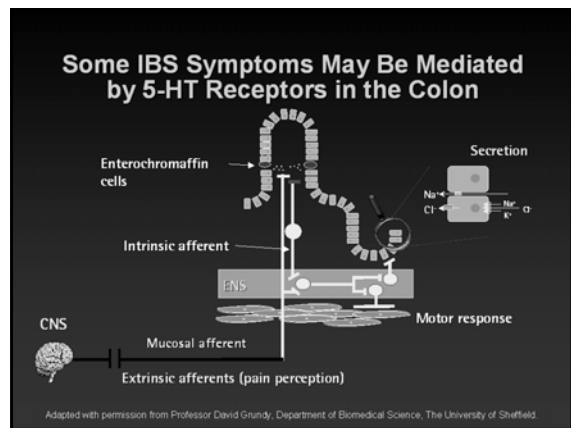
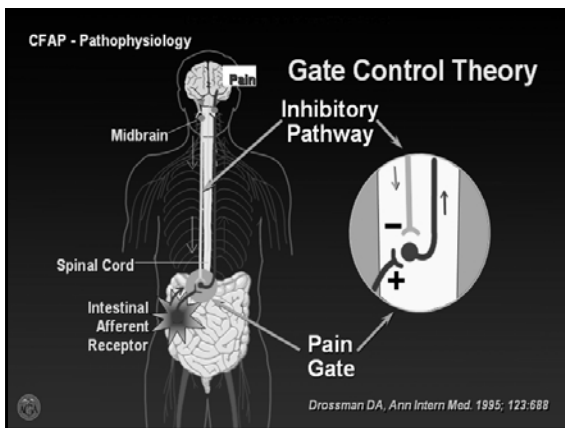
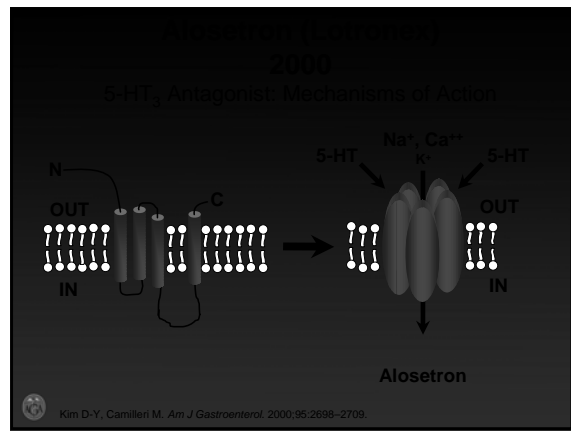
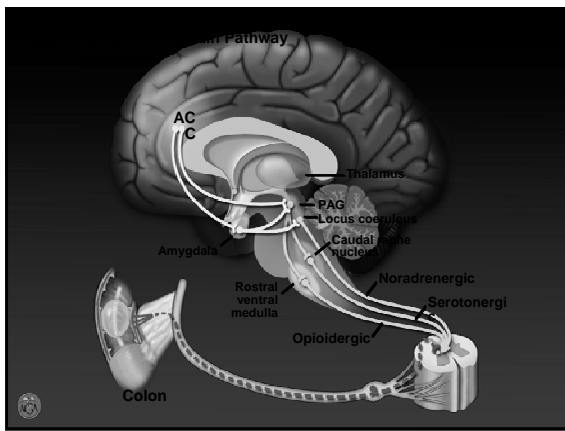
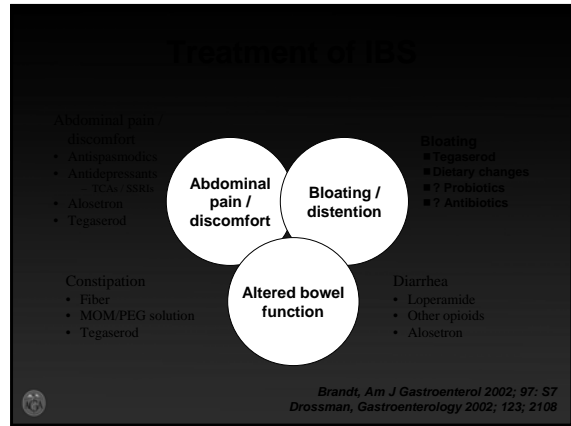
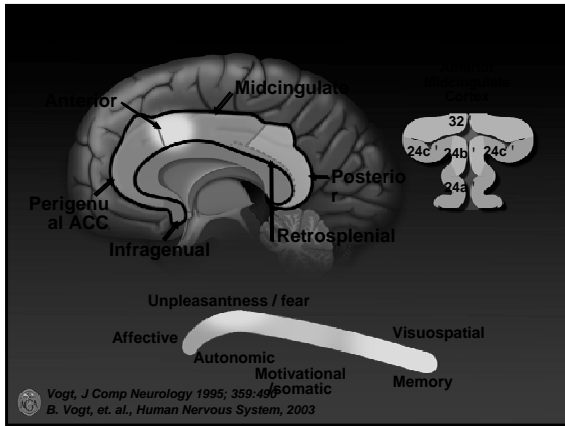
Drossman et al, *Gastroenterology* 1997; 112: 2120

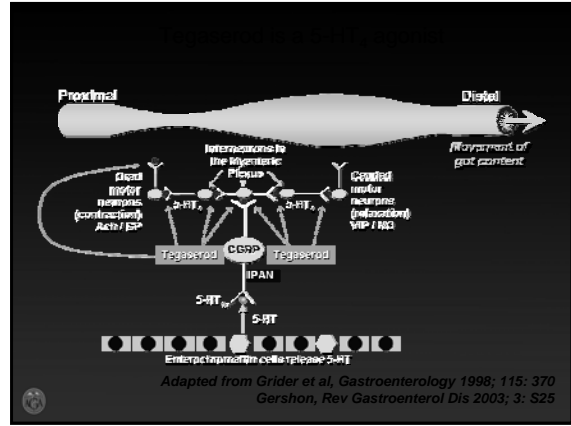
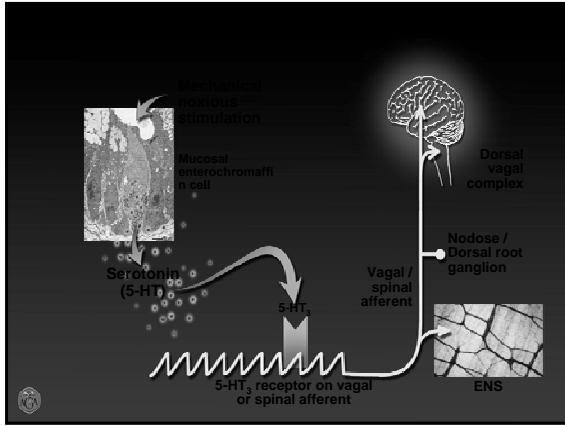




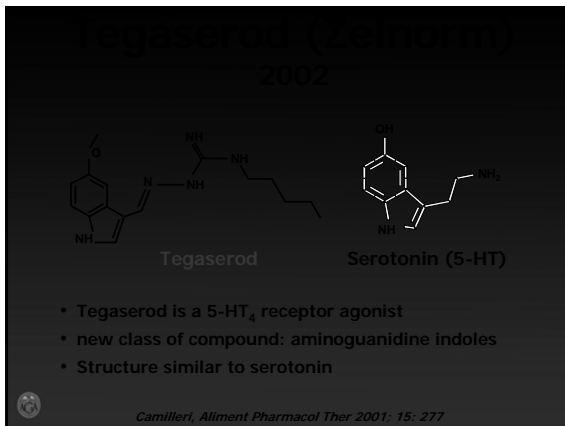
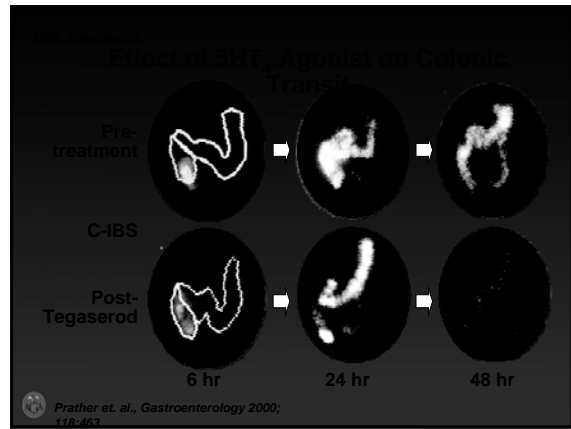
- Motility and visceral sensitivity
- | | |
|---------------------------------|-----------------------------------|
| Motility: | Visceral sensitivity: |
| ■ Serotonin | ■ Serotonin |
| ■ Acetylcholine | ■ Tachykinins |
| ■ Nitric oxide | ■ Calcitonin gene-related peptide |
| ■ Substance P | ■ Neurokinin A |
| ■ Vasoactive intestinal peptide | ■ Enkephalins |
| ■ Cholecystokinin | |
- Kim et al, Am J Gastroenterol 2000; 95: 2698
Grider et al, Gastroenterology 1998; 115: 370







- ### 5-HT₃ receptor antagonists
- Delay small bowel and colonic transit^{1,2}
 - treat diarrhea
 - Increase colonic compliance¹
 - improve fecal urgency
 - Inhibit chloride secretion¹
 - make stools more formed
 - Blunt the gastrocolonic response¹
 - improve urgency
 - Affect visceral afferent¹
 - 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.



Effect of tegaserod on additional dysmotility symptoms of IBS-C¹

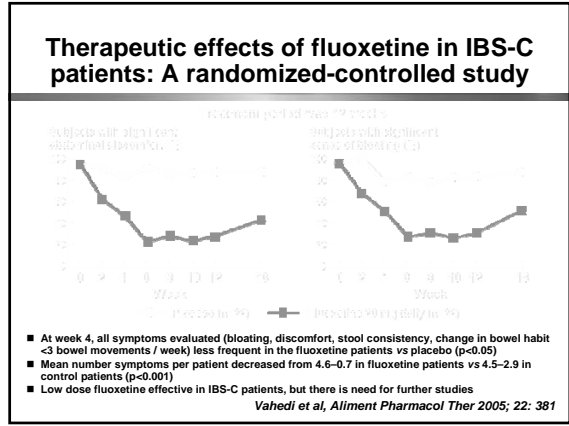
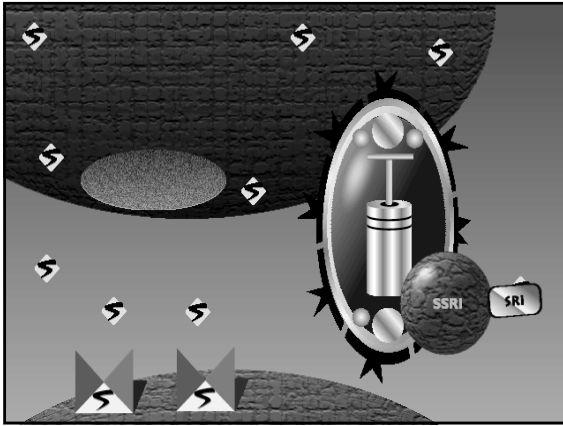
- ↑ Improved stool consistency
- ↑ Increased number of BMs/wk
- ↓ Reduced straining
- ↓ Relieved bloating
- ↓ Reduced abdominal pain / discomfort

■ 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 placebo²

■ Efficacy beyond 12 weeks has not been studied

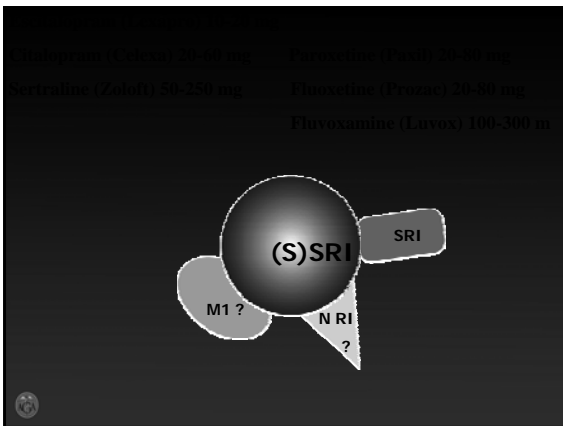
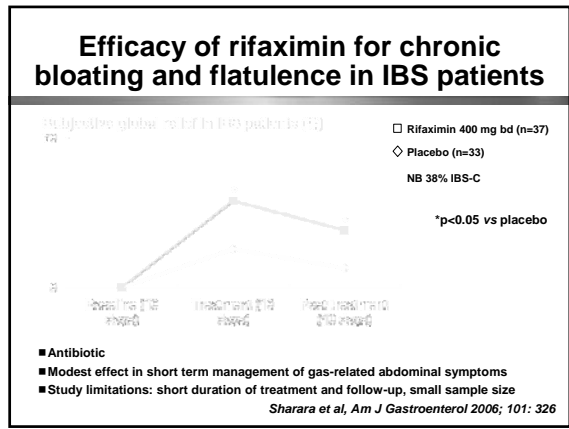
■ Response rates vs placebo were greater at month 1 than at month 3

¹Kellow et al, *Gut* 2003; 52: 671
²Patrick 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




CHRONIC CONSTIPATION IDIOPATHIC

Prevalence and incidence of constipation in the US

■ **Prevalence:**

- estimated 55 million Americans (prevalence 28%)¹
 - men 12%²
 - women 16%²
 - elderly individuals 40%³




2-28%

■ **Onset rate 40 / 1000 person-years⁴**


¹Locke et al, *Gastroenterology* 2000; 119: 1766
²Stewart et al, *Am J Gastroenterol* 1999; 94(12): 3530
³Talley et al, *Am J Gastroenterol* 1998; 91: 19
⁴Talley et al, *Am J Epidemiol* 1992; 136: 165

Measurement of colonic transit: Distribution of radiographic markers




A

Normal
SS markers remain



B

Slow-transit
Rings are scattered throughout the colon



C

Functional outlet obstruction
Rings are gathered in the rectosigmoid

Falgel et al, *Clin Cornerstone* 2002; 4: 11

Overlap in IBS-C and chronic constipation (CC)

At least 12 weeks, which need not be consecutive, in the preceding 12 months:

IBS-C

- Abdominal pain / discomfort associated with two or more of the following:
 - <3 BMs per week
 - hard or lumpy stools
 - relieved with BM
- May also be associated with:
 - bloating, feeling of abdominal distension, passage of mucus, straining
 - incomplete evacuation
 - may alternate with diarrhea

CC


- Two or more of the following:
 - <3 BMs per week
 - >25% of BMs:
 - hard or lumpy stool
 - straining
 - incomplete evacuation
 - sensation of anorectal obstruction / blockage
 - manual maneuvers to facilitate

BM = bowel movement

Thompson et al, *Gut* 1999; 45: 1143

Manometry in patients with dyssynergia

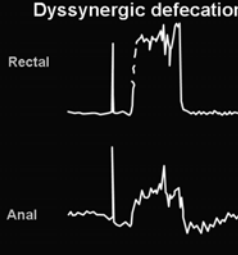
Normal



Rectal

Anal

Dyssynergic defecation

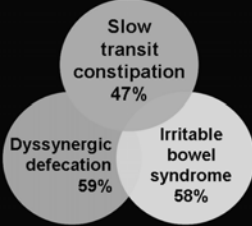


Rectal

Anal

Rao, *Gastroenterol Clin North Am* 2003; 32: 659

Functional subtypes of idiopathic constipation

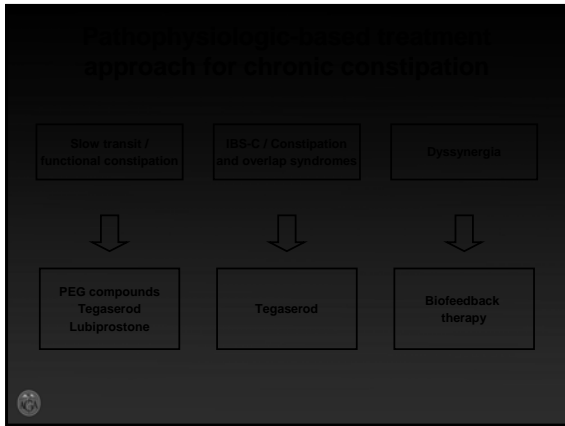


■ Slow-transit and IBS-C overlap in half of each group

Rao et al, *Gastroenterol Clin North Am* 2003; 32: 659
Mertz et al, *Am J Gastroenterol* 1999; 94: 609

Summary: Pathophysiology of chronic constipation

- **Slow-transit constipation:**
 - impaired colonic and rectosigmoid contractile response
 - reduced colonic propulsion of stool with slower transit
 - fewer serotonin cells in the colon
 - abnormalities in serotonin receptor protein
 - absent or decreased number of interstitial cells of Cajal
- **Dyssynergic defecation:**
 - impaired co-ordination of muscles involved in defecation
 - impaired sensation
- **IBS with constipation:**
 - primary complaint is abdominal pain
 - altered release and re-uptake of serotonin

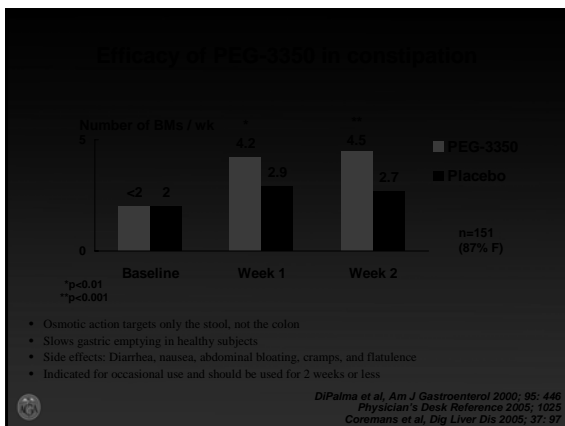
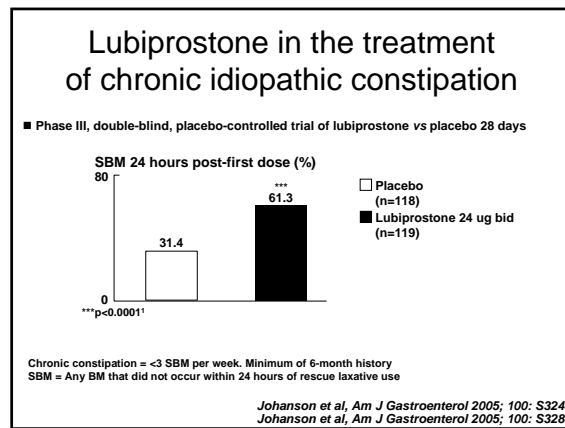
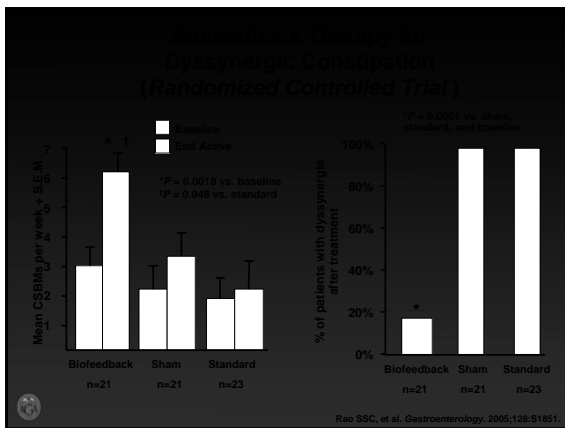


Summary: Tegaserod in chronic constipation

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



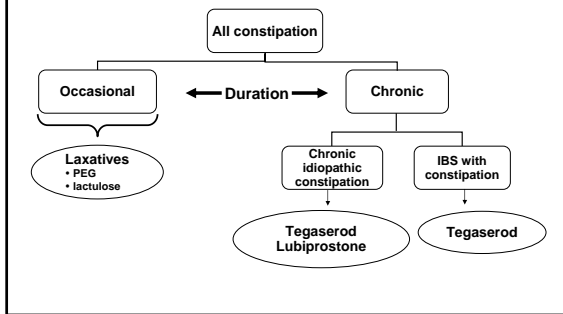
Comparison of lubiprostone and tegaserod in CC

	Lubiprostone ¹	Tegaserod ²
Description	Chloride channel activator	5-HT ₄ 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 ^{3,4†}	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%)

¹Lubiprostone PI
²Tegaserod PI
³Johanson, Am J Gastroenterol 2005; 100: S324
⁴Kamm, Am J Gastroenterol 2005; 100: 362

*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%)

FDA-approved prescription medications for constipation



THE END