

Irritable Bowel Syndrome and Chronic Constipation

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What is IBS?

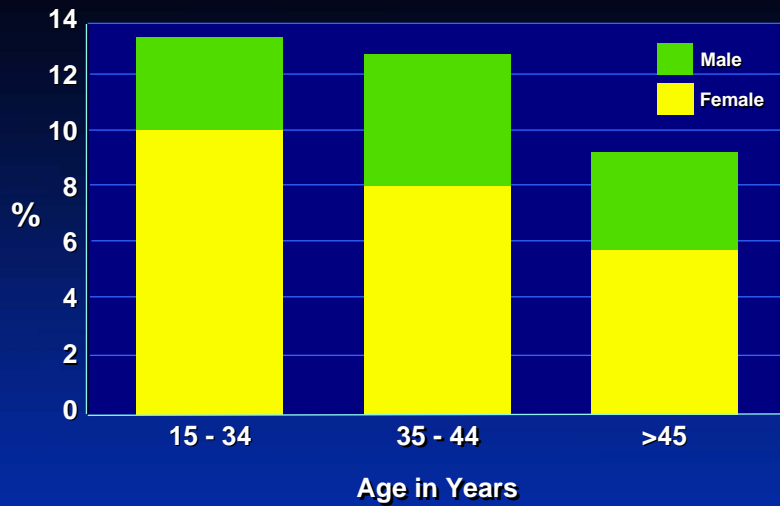
- a chronic, intermittent gastrointestinal condition
- a functional bowel disorder without evidence of structural or biochemical abnormalities
- characterized by abdominal pain or discomfort associated with altered bowel function:
 - diarrhea: >3BMs/day, loose stools, urgency
 - constipation: <3BMs/wk,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

Drossman et al, Gastroenterology 1997; 112: 2120



IBS - Epidemiology

U.S. Prevalence



Drossman DA, et al., *Dig Dis Sci* 1993; 38:1569

IBS - Physiologic Research

Stress affects
GI function

Pain
sensitivit
y

Clustered
contractions
CNS / ENS
Autonomic
reactivity

Meals
Pain / motility

3 cpm
motility

Visceral
hypersensitivity

Post-infectious
IBS

1950 1960 1970 1980 1990 2000 →

Mechanisms

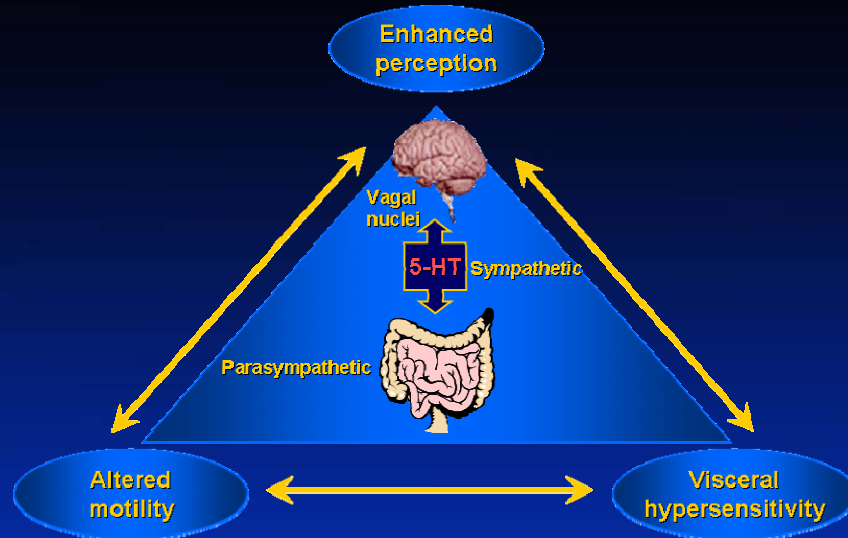
Motility

Brain-Gut
Interactions
Myoelectrical Marker

Inflammation

Visceral Hypersensitivity

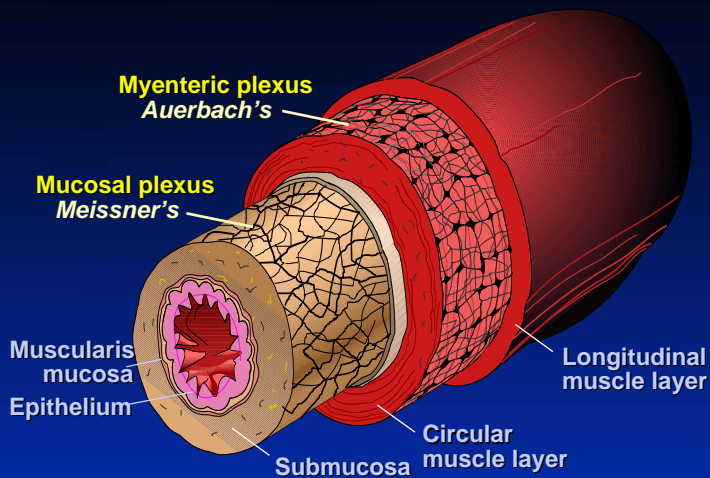
Brain-gut connection in IBS



Adapted from Camilleri and Choi, *Aliment Pharmacol Ther* 1997; 11: 3
Hunt and Tougas, *Best Prac and Research Clin Gastroenterol* 2002; 16: 869

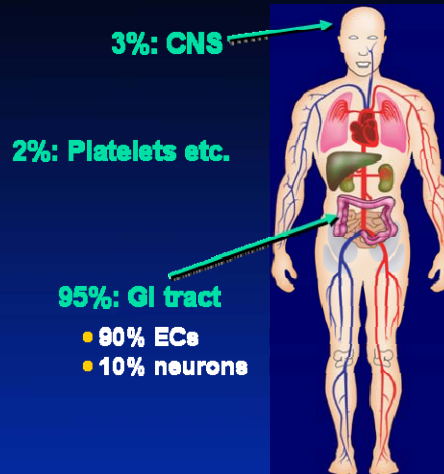
IBS - Pathophysiology

Enteric Nervous System Anatomy



Goyal RK, Hirano I, *New Engl J Med*. 1996; 334:1106

Physiologic distribution of serotonin (5-HT)



After Wood JD, *Gastroenterol Endosc News* 2000; (Suppl): S1

Some possible mediators of motility and visceral sensitivity

Motility:

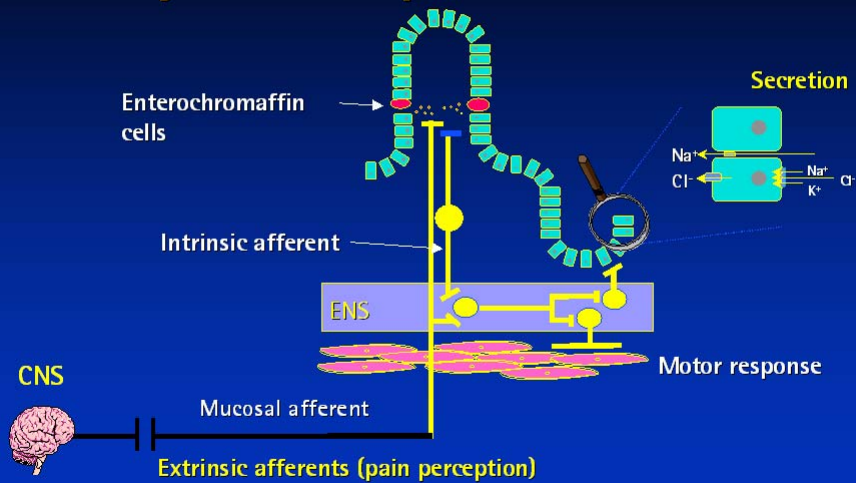
- Serotonin
- Acetylcholine
- Nitric oxide
- Substance P
- Vasoactive intestinal peptide
- Cholecystokinin

Visceral sensitivity:

- Serotonin
- Tachykinins
- Calcitonin gene-related peptide
- Neurokinin A
- Enkephalins

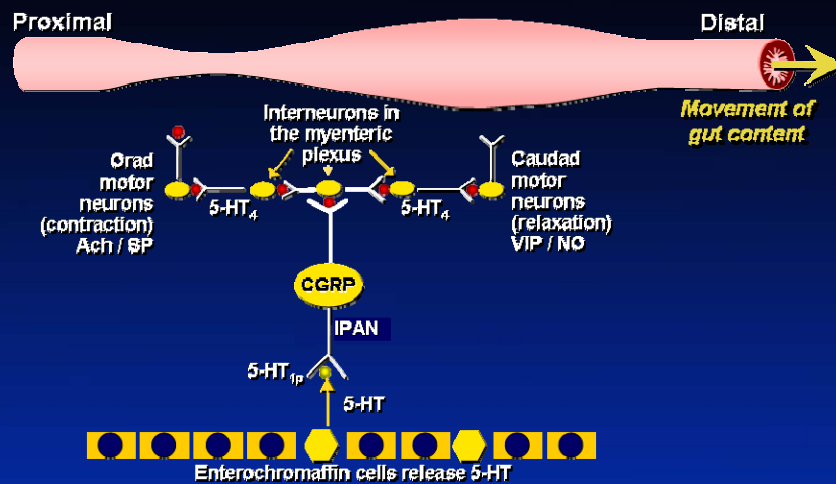
Kim et al, *Am J Gastroenterol* 2000; 95: 2698
Grider et al, *Gastroenterology* 1998; 115: 370

Some IBS Symptoms May Be Mediated by 5-HT Receptors in the Colon



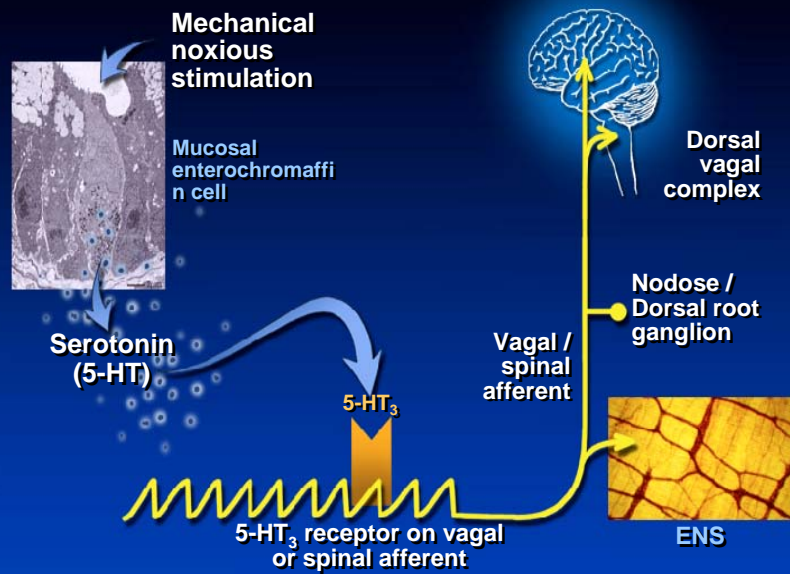
Adapted with permission from Professor David Grundy, Department of Biomedical Science, The University of Sheffield.

Serotonin (5-HT) and motor activity

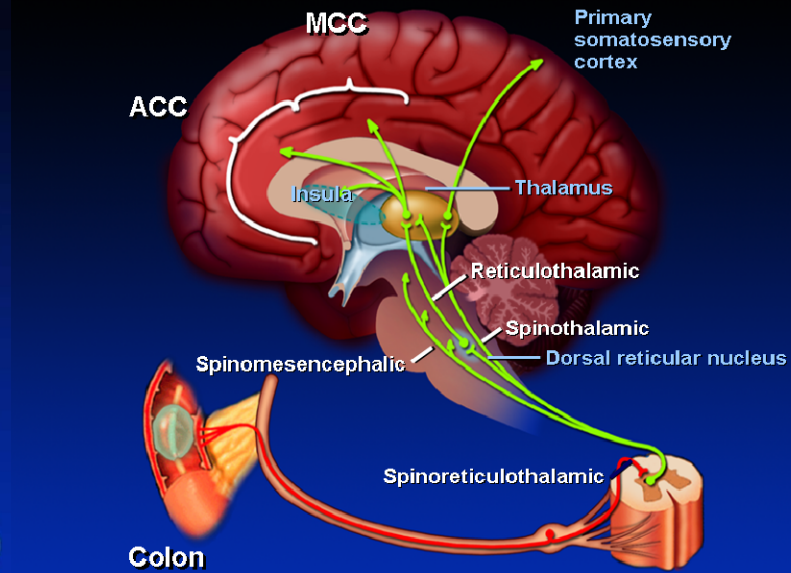


Adapted from Grider et al, *Gastroenterology* 1998; 115: 370
Gershon, *Rev Gastroenterol Dis* 2003; 3: S25

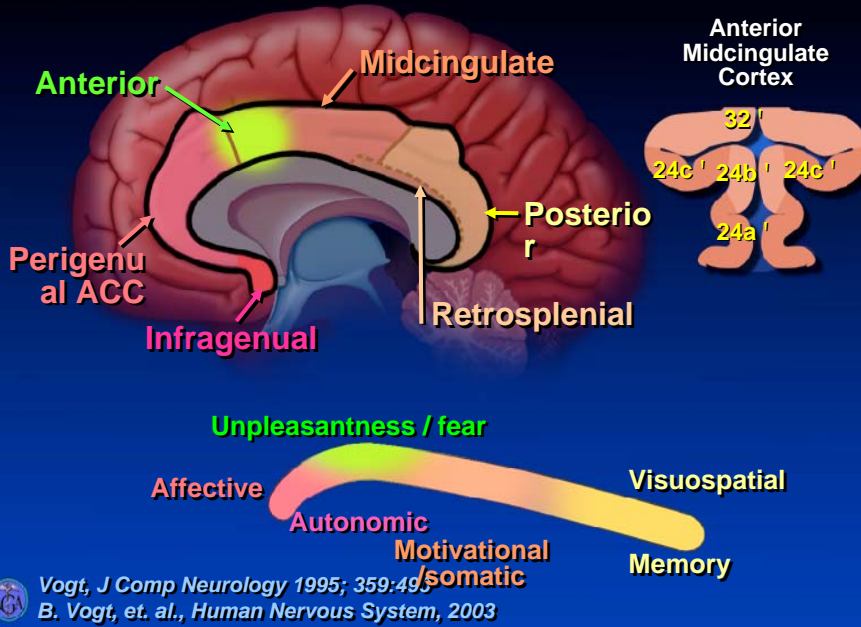
IBS - Serotonin Receptors on Sensory Afferents



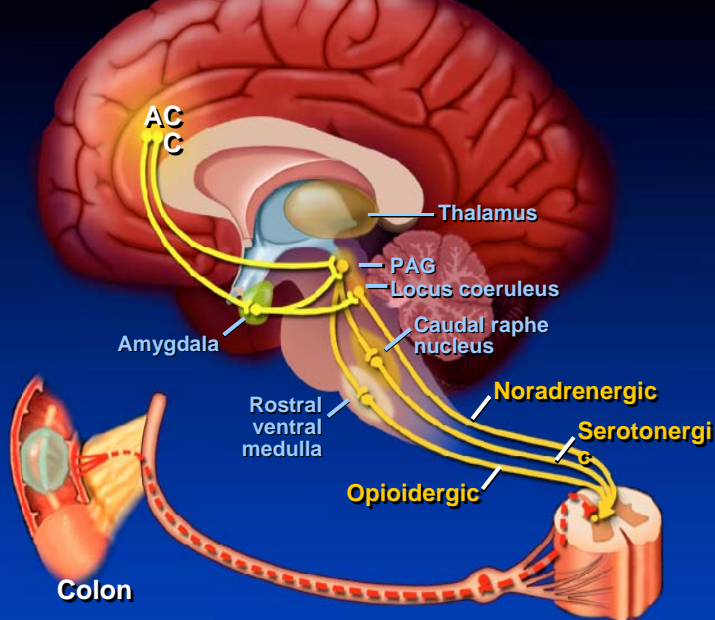
Brain-gut interactions modulating visceral motor and sensory responses

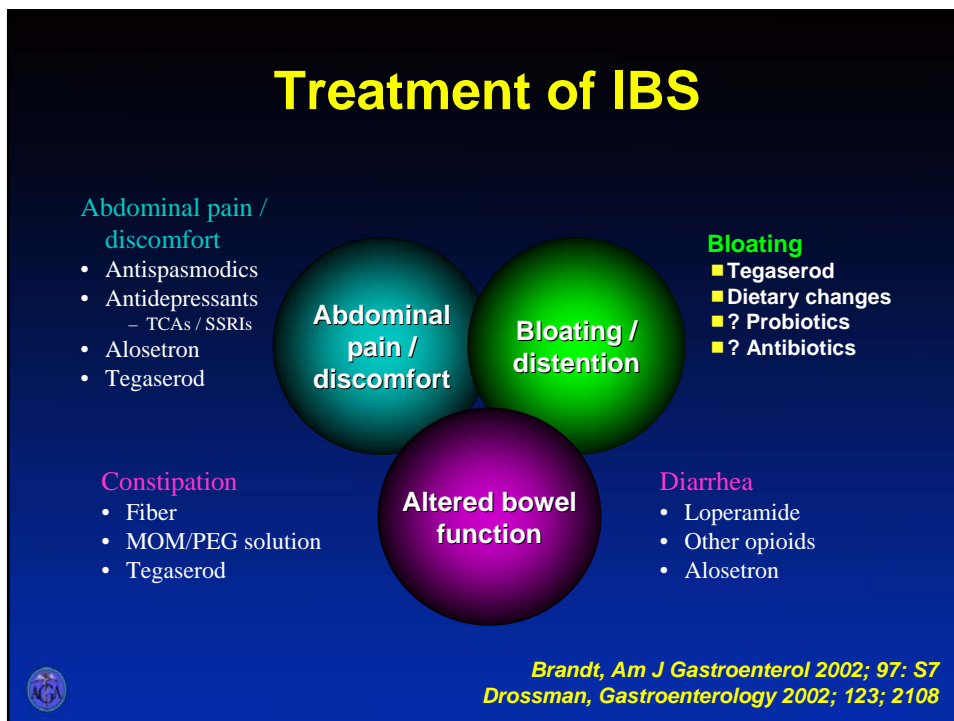
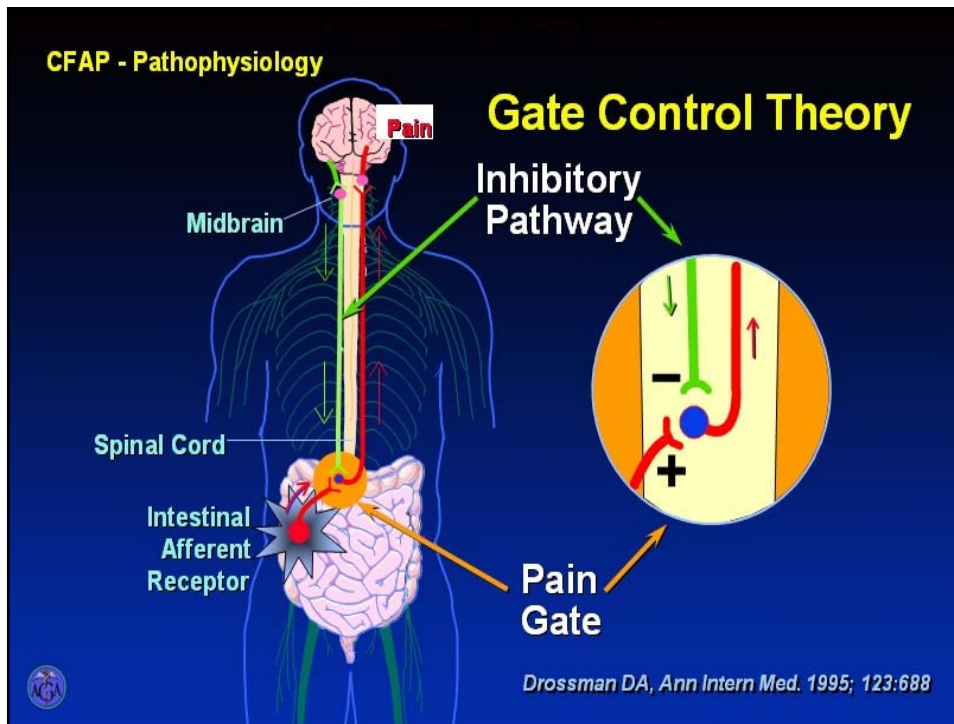


IBS - Cingulate Cortex - Functional Associations



Descending Visceral Pain Pathway

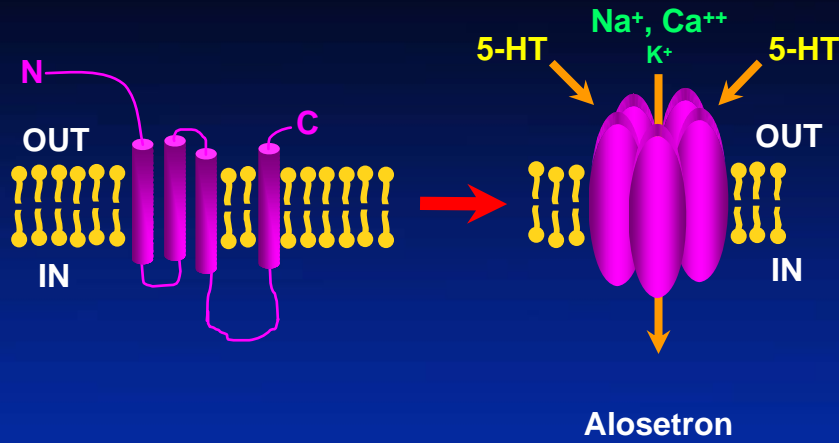




Alosetron (Lotronex)

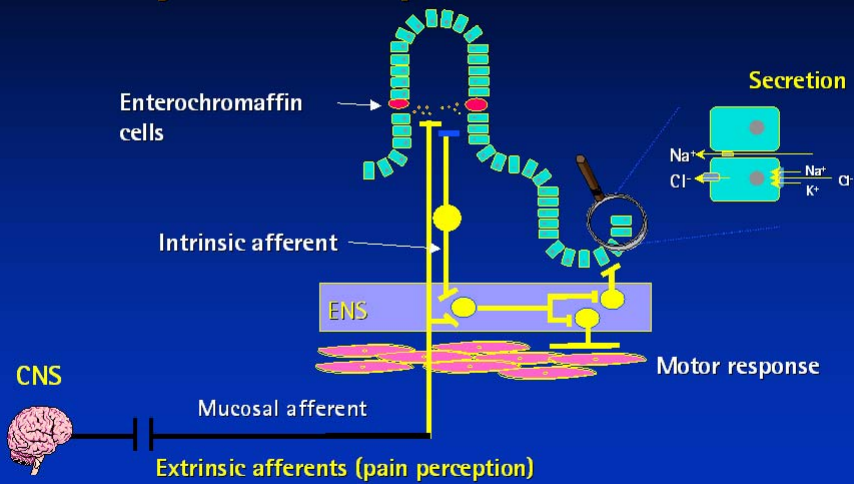
2000

5-HT₃ Antagonist: Mechanisms of Action



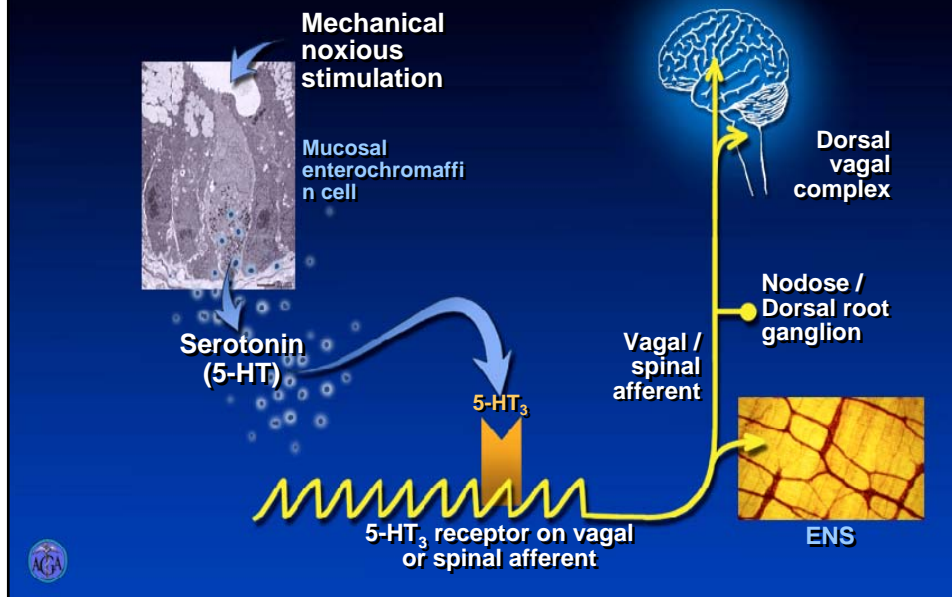
Kim D-Y, Camilleri M. *Am J Gastroenterol.* 2000;95:2698–2709.

Some IBS Symptoms May Be Mediated by 5-HT Receptors in the Colon



Adapted with permission from Professor David Grundy, Department of Biomedical Science, The University of Sheffield.

IBS - Serotonin Receptors on Sensory Afferents



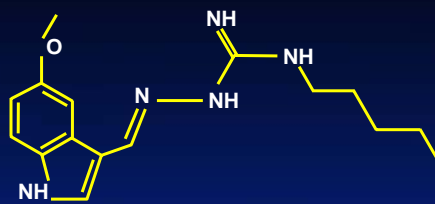
Mechanisms of Action of 5-HT₃ receptor antagonists

- 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

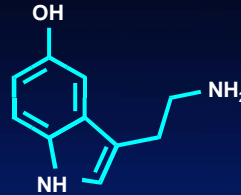


1. Kim D-Y, Camilleri M. *Am J Gastroenterol*. 2000;95:2698–2709.
2. Viramontes BE et al. *Am J Gastroenterol*. 2001;96:2671–2676.

Tegaserod (Zelnorm) 2002



Tegaserod



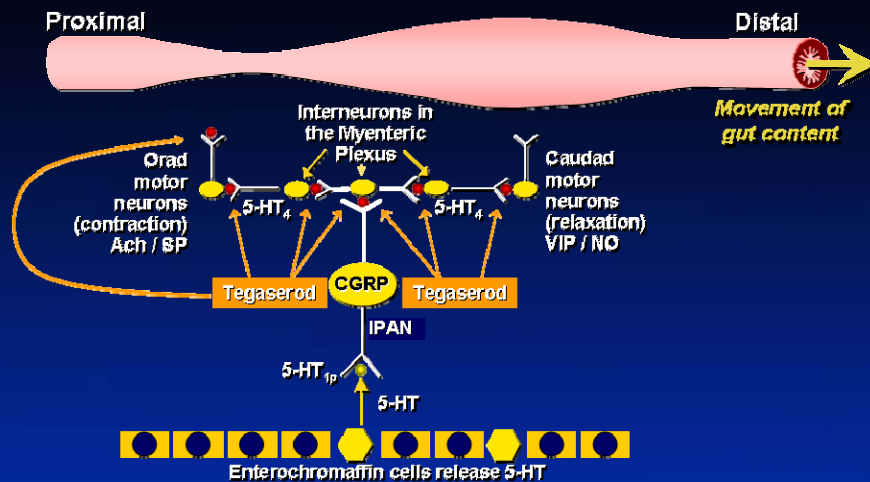
Serotonin (5-HT)

- Tegaserod is a 5-HT₄ receptor agonist
- new class of compound: aminoguanidine indoles
- Structure similar to serotonin

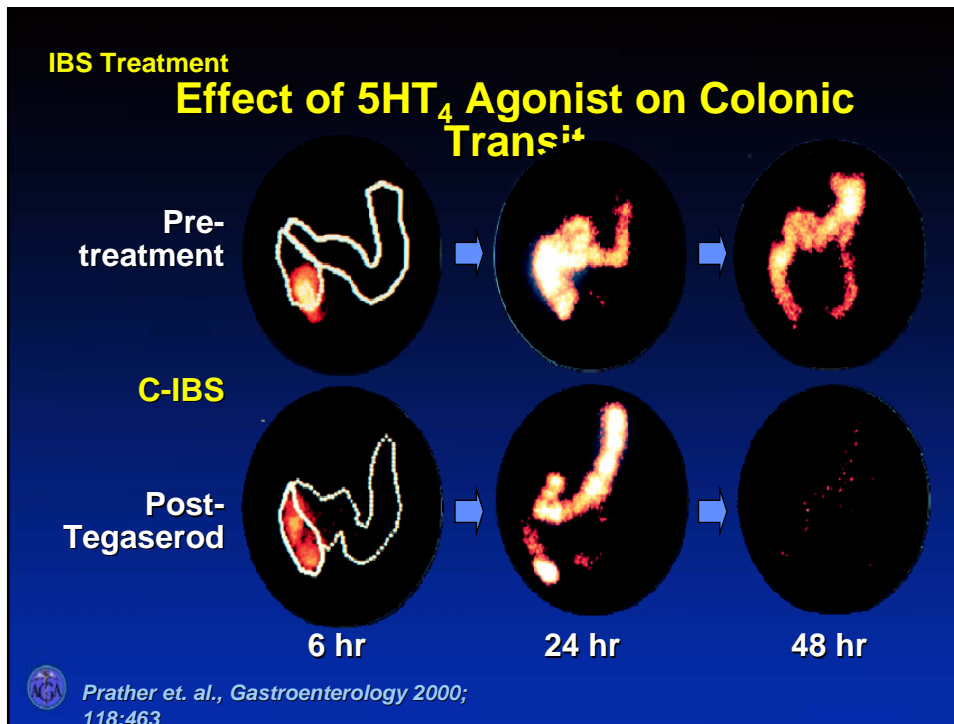


Camilleri, Aliment Pharmacol Ther 2001; 15: 277

Tegaserod is a 5-HT₄ agonist



Adapted from Grider et al, Gastroenterology 1998; 115: 370
Gershon, Rev Gastroenterol Dis 2003; 3: S25

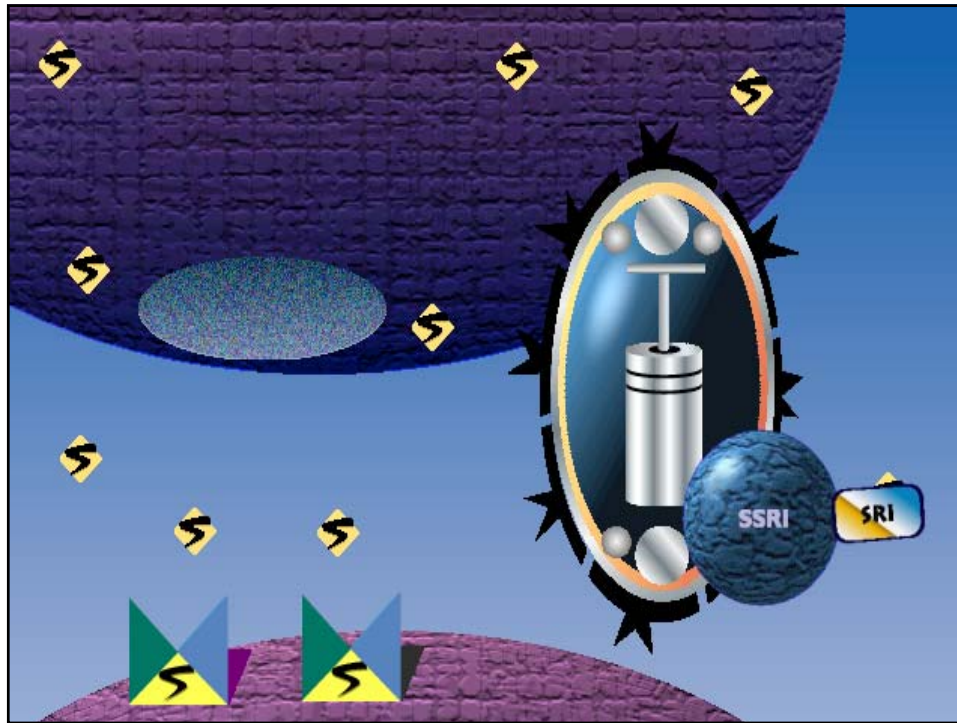


Effect of tegaserod on additional dysmotility symptoms of IBS-C¹

- ↑ 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



Serotonin Transporter (SERT)

- 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



Escitalopram (Lexapro) 10-20 mg

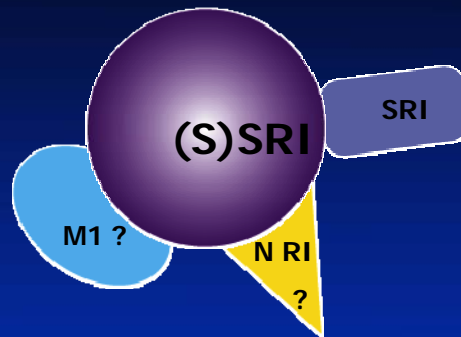
Citalopram (Celexa) 20-60 mg

Sertraline (Zoloft) 50-250 mg

Paroxetine (Paxil) 20-80 mg

Fluoxetine (Prozac) 20-80 mg

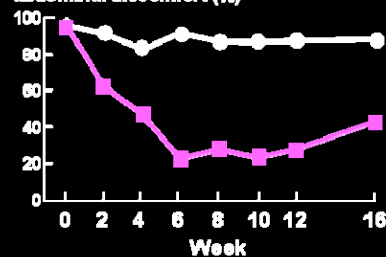
Fluvoxamine (Luvox) 100-300 mg



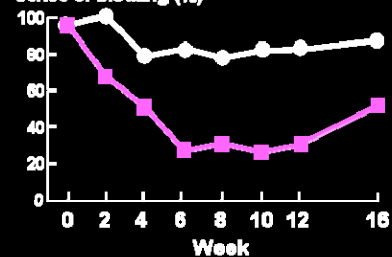
Therapeutic effects of fluoxetine in IBS-C patients: A randomized-controlled study

Treatment period was 12 weeks

Subjects with significant abdominal discomfort (%)



Subjects with significant sense of bloating (%)



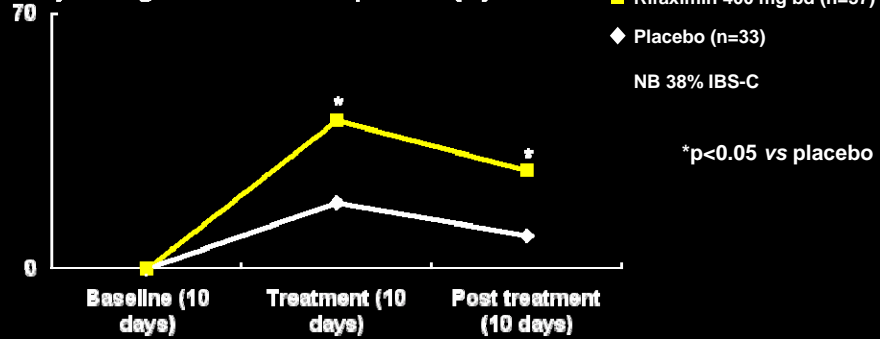
—●— Placebo (n=22) —■— Fluoxetine 20 mg daily (n=22)

- 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

Subjective global relief 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

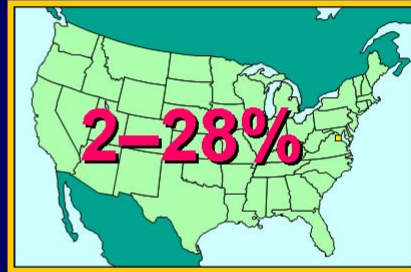
IDIOPATHIC



Prevalence and incidence of constipation in the US

■ Prevalence:

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



■ 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* 1996; 91: 19

⁴Talley et al, *Am J Epidemiol* 1992; 136: 165

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

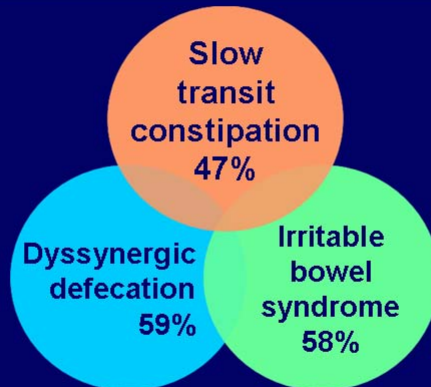
CC

- 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

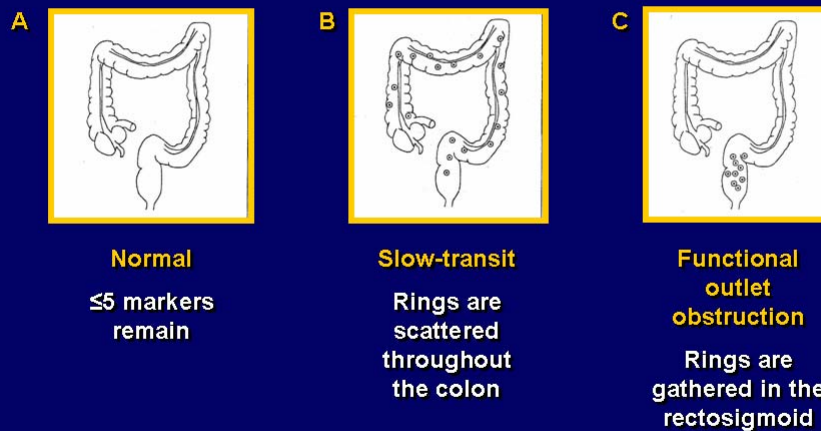
Functional subtypes of idiopathic constipation



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

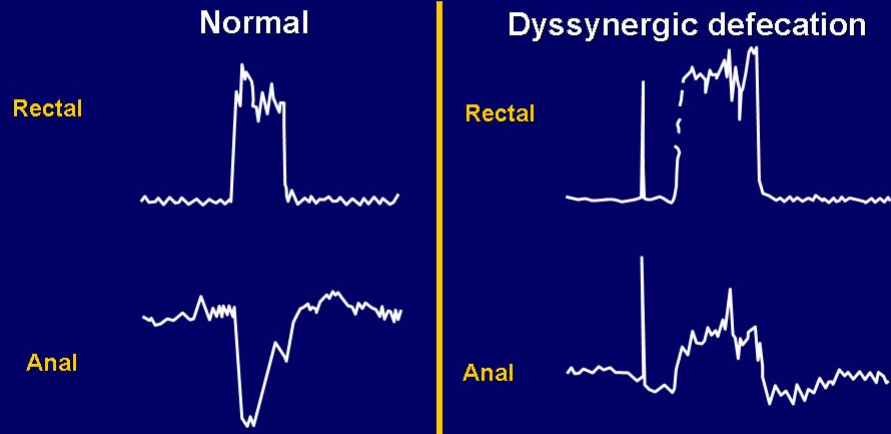
Rao et al, Gastroenterol Clin North Am 2003; 32: 659
Mertz et al, Am J Gastroenterol 1999; 94: 609

Measurement of colonic transit: Distribution of radiographic markers



Faigel et al, Clin Cornerstone 2002; 4: 11

Manometry in patients with dyssynergia

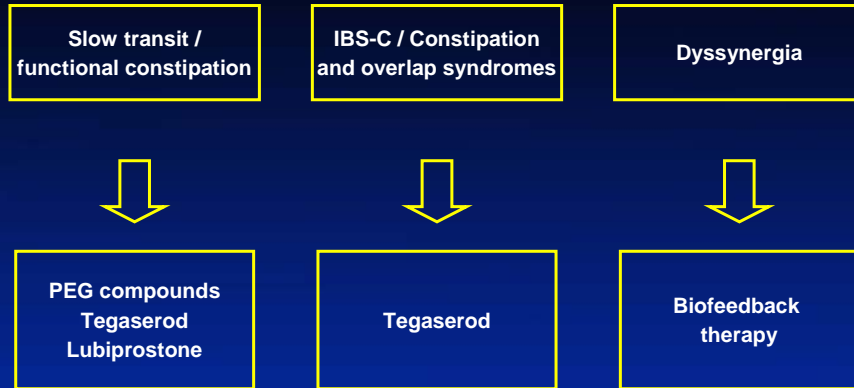


Rao, Gastroenterol Clin North Am 2003; 32: 659

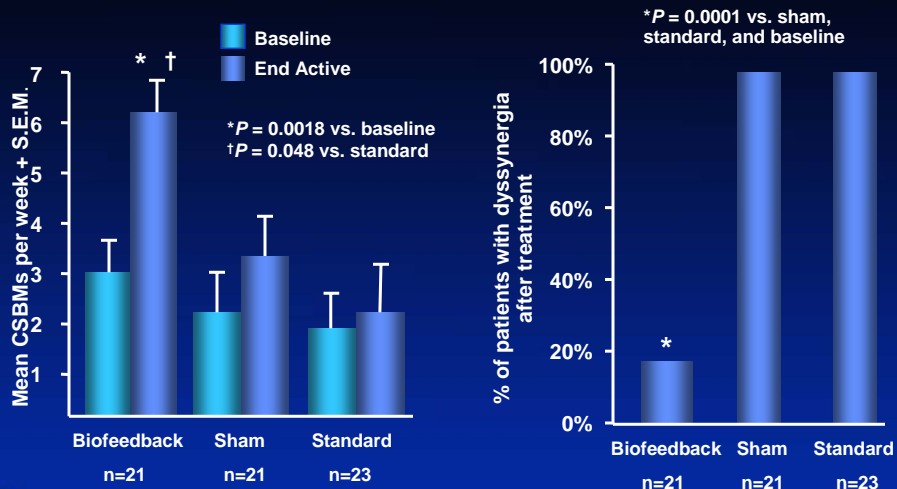
Summary: Pathophysiology of chronic constipation

- **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

Pathophysiologic-based treatment approach for chronic constipation

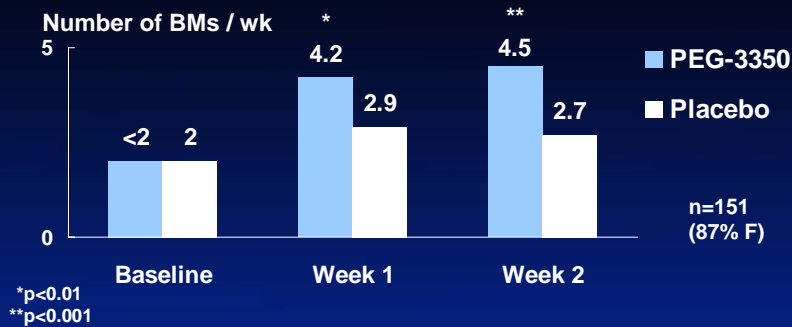


Biofeedback Therapy for Dyssynergic Constipation (Randomized Controlled Trial)



Rao SSC, et al. *Gastroenterology*. 2005;128:S1851.

Efficacy of PEG-3350 in constipation



- Osmotic action targets only the stool, not the colon
- Slows gastric emptying in healthy subjects
- Side effects: Diarrhea, nausea, abdominal bloating, cramps, and flatulence
- Indicated for occasional use and should be used for 2 weeks or less



DiPalma et al, Am J Gastroenterol 2000; 95: 446
Physician's Desk Reference 2005; 1025
Coremans et al, Dig Liver Dis 2005; 37: 97

Summary: Tegaserod in chronic constipation

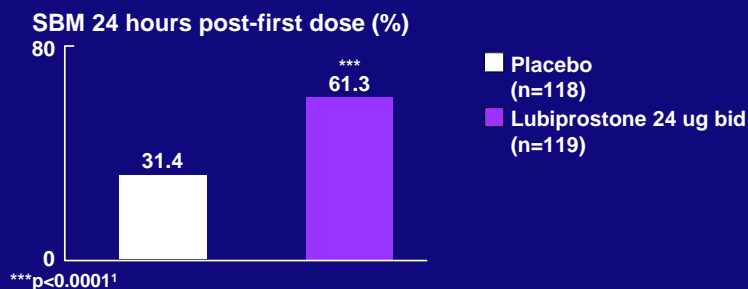
In chronic constipation, tegaserod:

- 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

Lubiprostone in the treatment of chronic idiopathic constipation

■ Phase III, double-blind, placebo-controlled trial of lubiprostone vs placebo 28 days



Chronic constipation = <3 SBM per week. Minimum of 6-month history
SBM = Any BM that did not occur within 24 hours of rescue laxative use

Johanson et al, Am J Gastroenterol 2005; 100: S324
Johanson et al, Am J Gastroenterol 2005; 100: S328

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 patients
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%)

¹Different 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%)

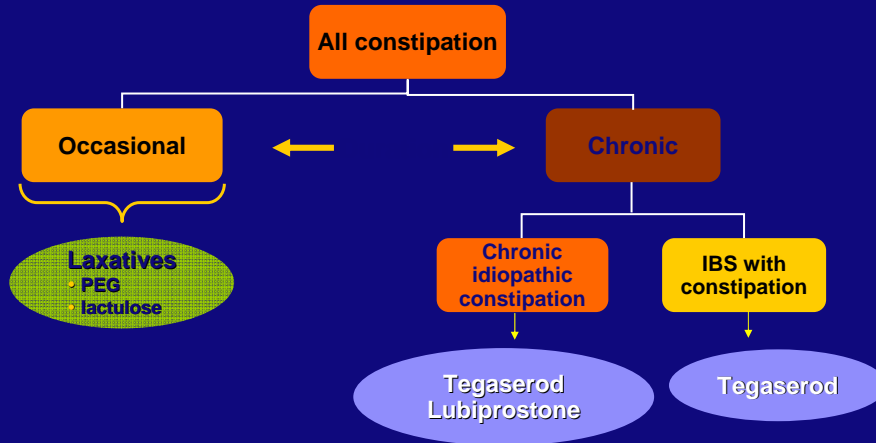
¹Lubiprostone PI

²Tegaserod PI

³Johanson, Am J Gastroenterol 2005; 100: S324

⁴Kamm, Am J Gastroenterol 2005; 100: 362

FDA-approved prescription medications for constipation



THE END