

Irritable Bowel Syndrome and Chronic Constipation

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What is IBS?

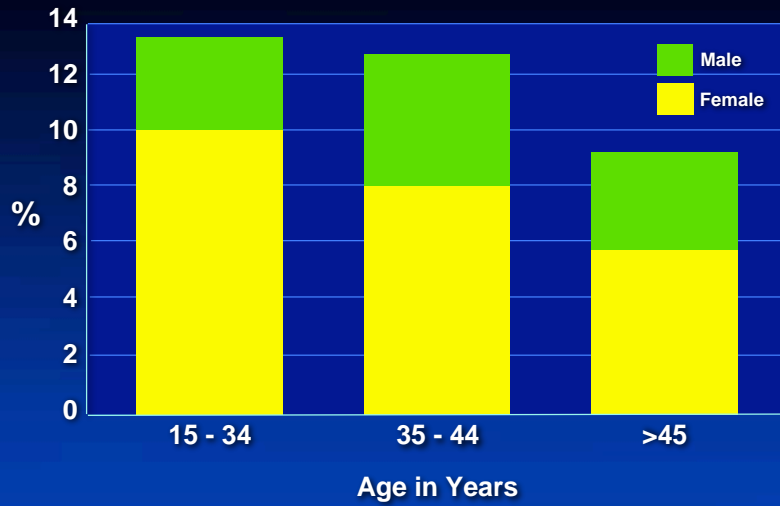
- a chronic, intermittent gastrointestinal condition
- a functional bowel disorder without evidence of structural or biochemical abnormalities
- characterized by **ABDOMINAL PAIN** or **DISCOMFORT** associated with altered bowel function:
 - diarrhea
 - constipation
 - bloating or feeling of distension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



Drossman et al, Gastroenterology 1997; 112: 2120

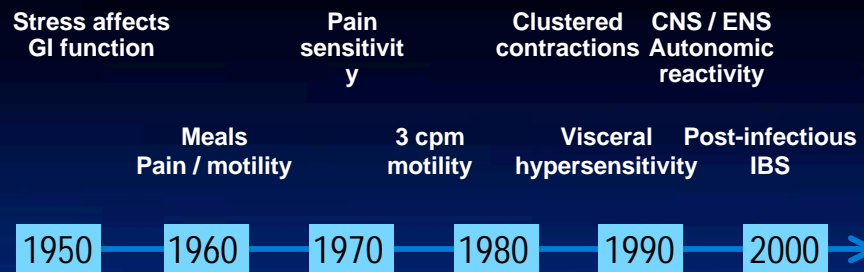
IBS - Epidemiology

U.S. Prevalence



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

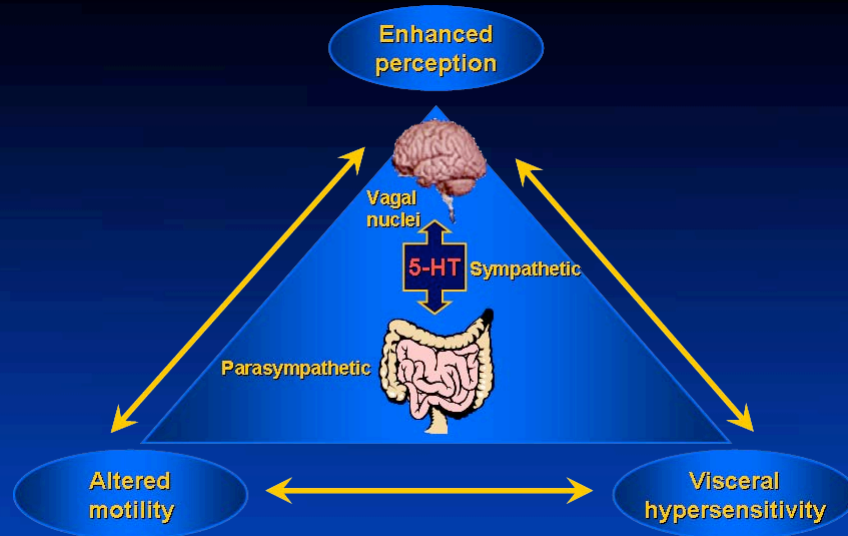
IBS - Physiologic Research



Mechanisms



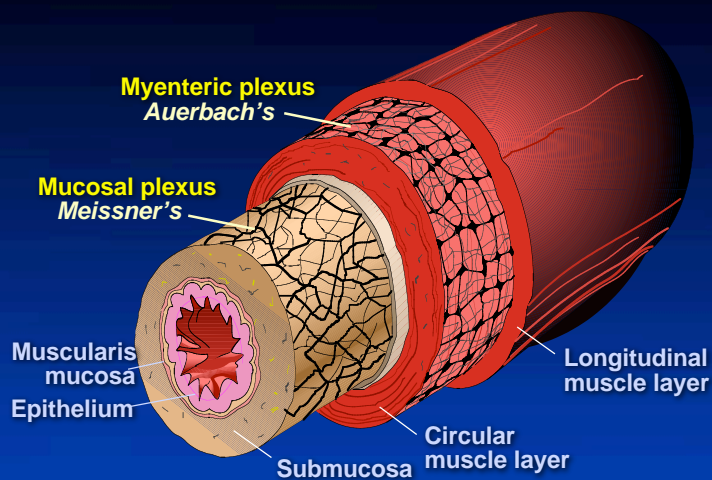
Brain-gut connection in IBS



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

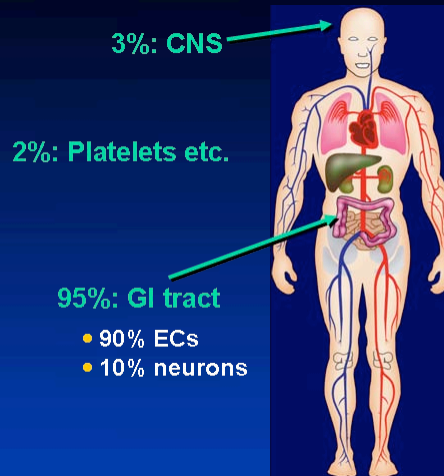
IBS - Pathophysiology

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:

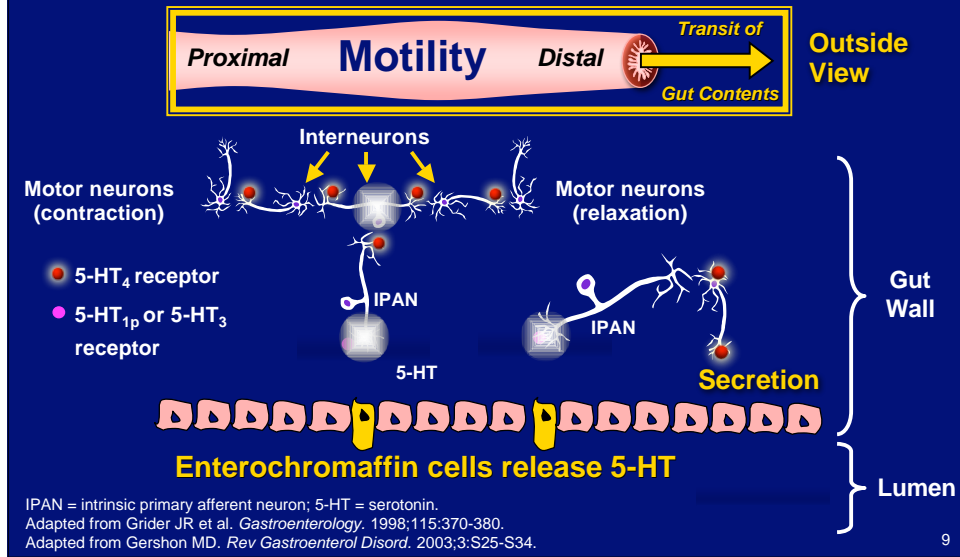
- Serotonin
- Acetylcholine
- Nitric oxide
- Substance P
- Vasoactive intestinal peptide
- Cholecystokinin

Visceral sensitivity:

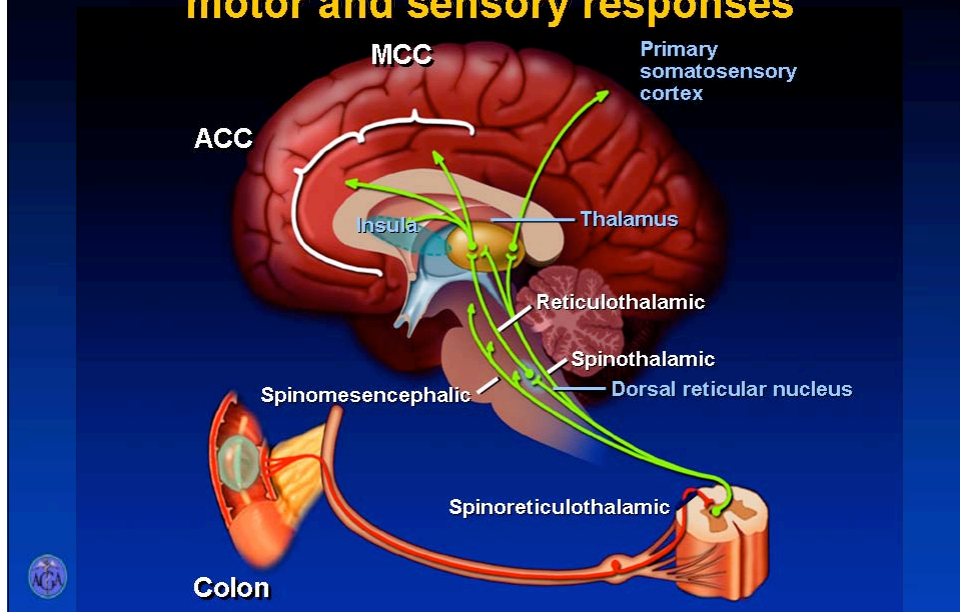
- Serotonin
- Tachykinins
- Calcitonin gene-related peptide
- Neurokinin A
- Enkephalins

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

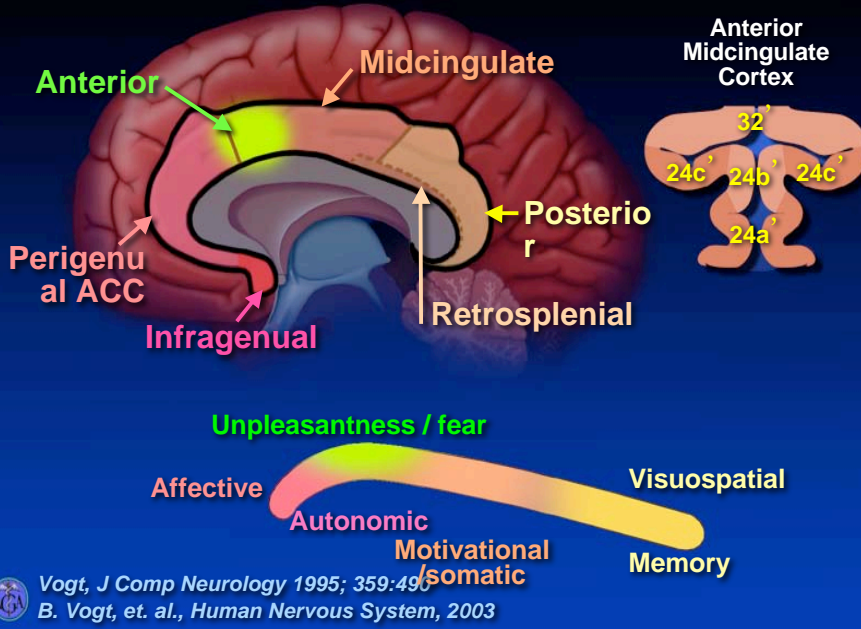
Serotonin Release Stimulates Motility and Secretion via Enteric Nerve Reflexes



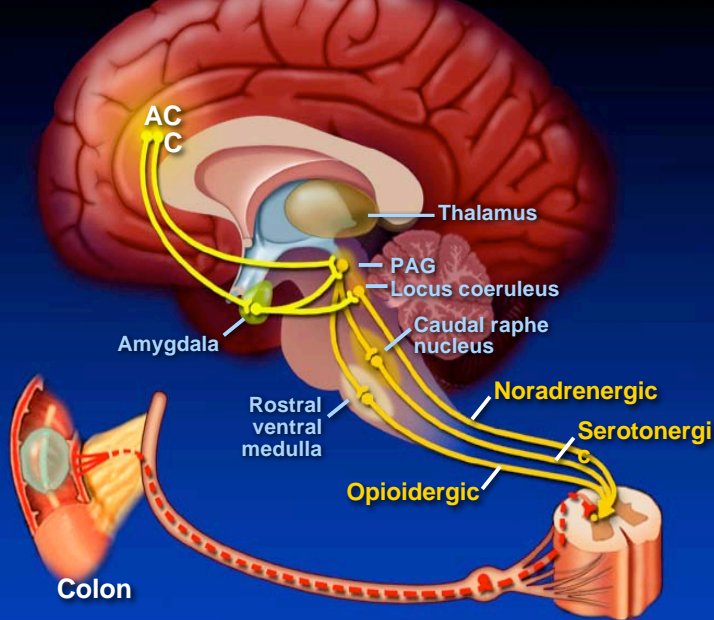
Brain-gut interactions modulating visceral motor and sensory responses

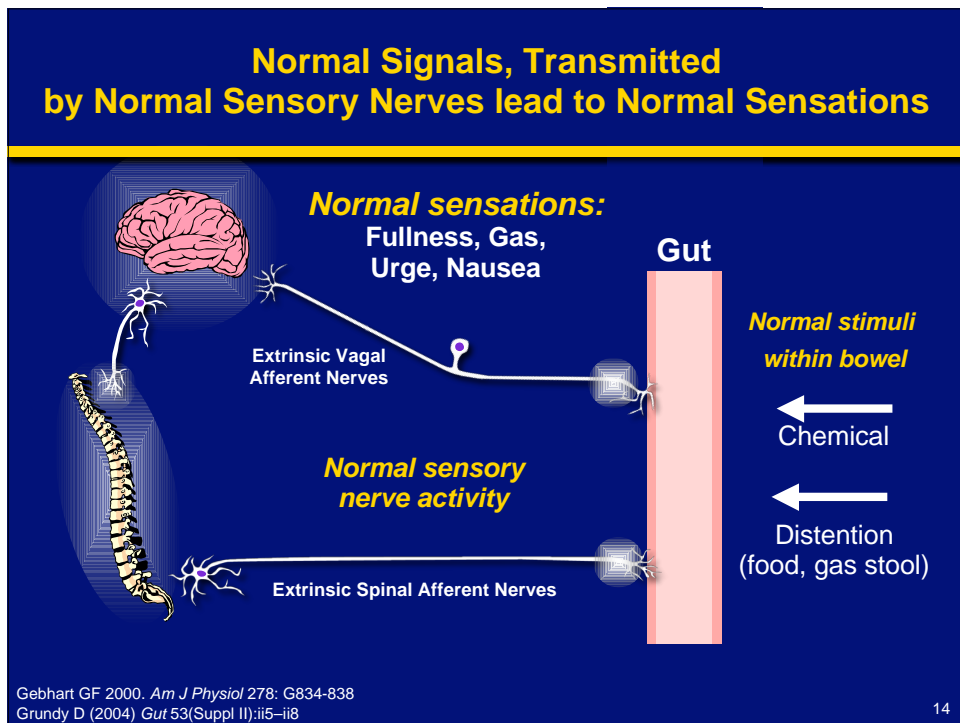
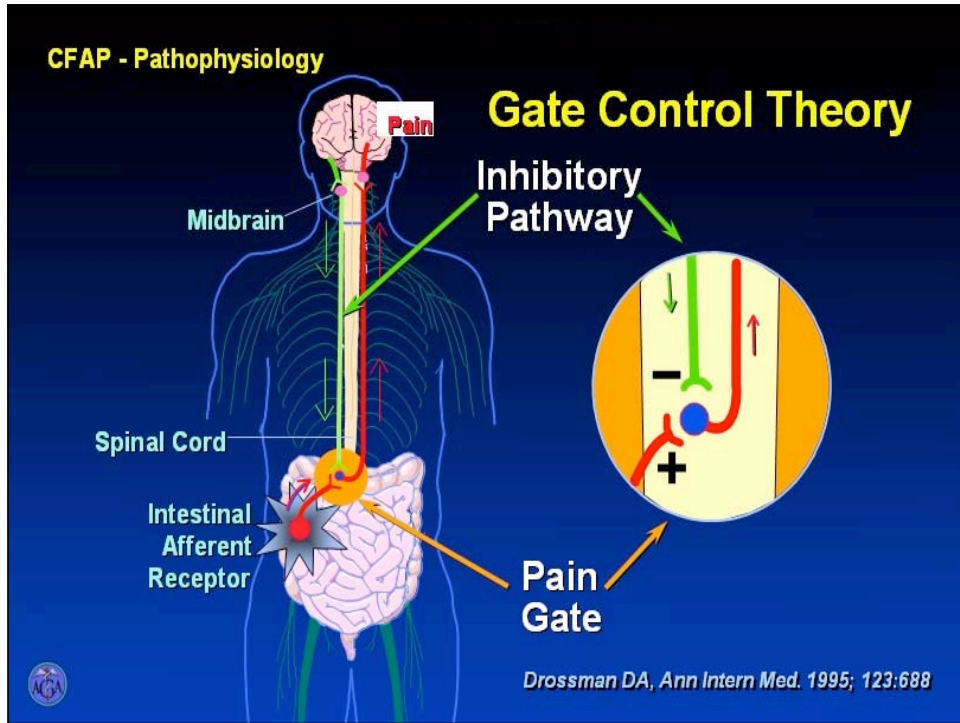


IBS - Cingulate Cortex - Functional Associations



Descending Visceral Pain Pathway





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

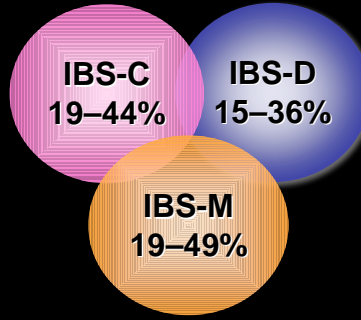
Longstreth et al, Gastroenterology 2006; 130:1480

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
Tillisch et al, Am J Gastroenterol 2005; 100: 896

Mearin et al, Eur J Gastroenterol Hepatol 2003; 15: 165
Drossman et al, Gastroenterology 2005; 128: 580

Treatment of IBS

Abdominal pain / discomfort

- Antispasmodics
- Antidepressants
 - TCAs / SSRIs
- Alosetron
- Tegaserod

Abdominal pain / discomfort

Bloating / distention

Bloating

- Tegaserod
- Dietary changes
- ? Probiotics
- ? Antibiotics

Constipation

- Fiber
- MOM/PEG solution
- Tegaserod

Altered bowel function

Diarrhea

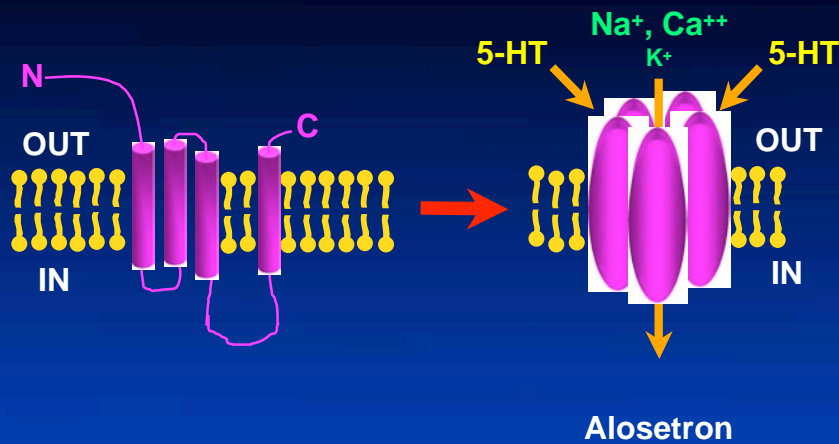
- Loperamide
- Other opioids
- Alosetron



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

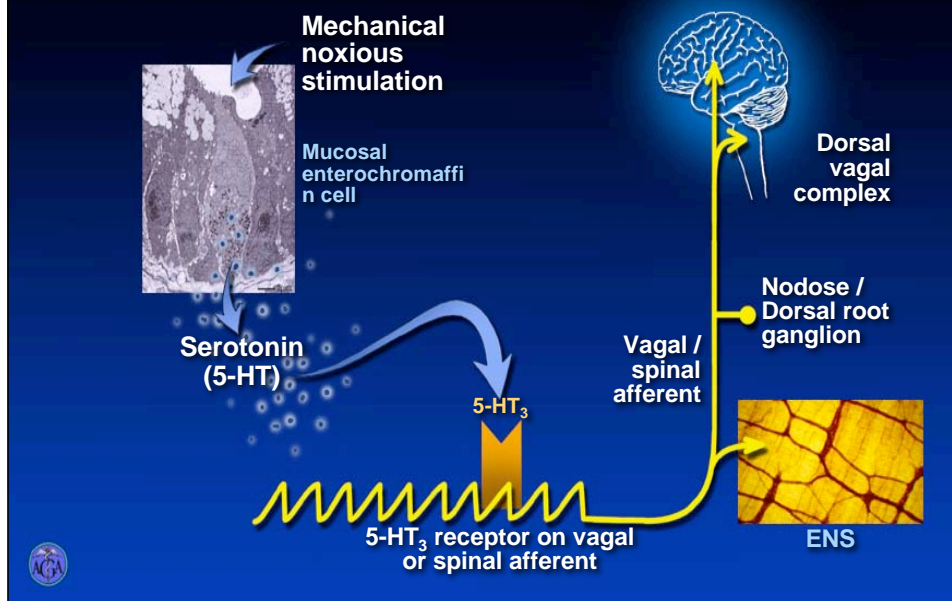
Alosetron (Lotronex) 2000

5-HT₃ Antagonist: Mechanisms of Action



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

IBS - Serotonin Receptors on Sensory Afferents



Mechanisms of Action of 5-HT₃ receptor antagonists

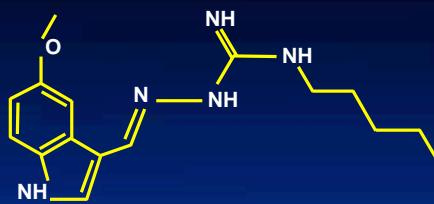
- Delay small bowel and colonic transit^{1,2}
 - treat diarrhea
- Increase colonic compliance¹
 - improve fecal urgency
- Inhibit chloride secretion¹
 - make stools more formed
- Blunt the gastrocolonic response¹
 - improve urgency
- Affect visceral afferent¹
 - diminish abdominal pain



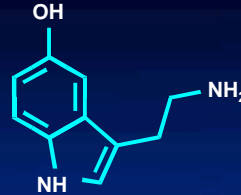
1. Kim D-Y, Camilleri M. *Am J Gastroenterol.* 2000;95:2698-2709.
2. Viramontes BE et al. *Am J Gastroenterol.* 2001;96:2671-2676.

Tegaserod (Zelnorm)

2002



Tegaserod



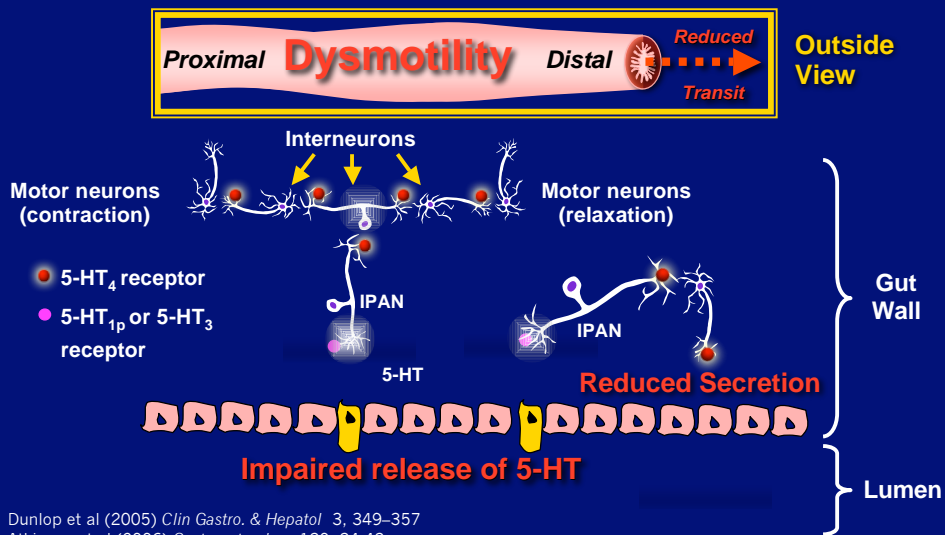
Serotonin (5-HT)

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

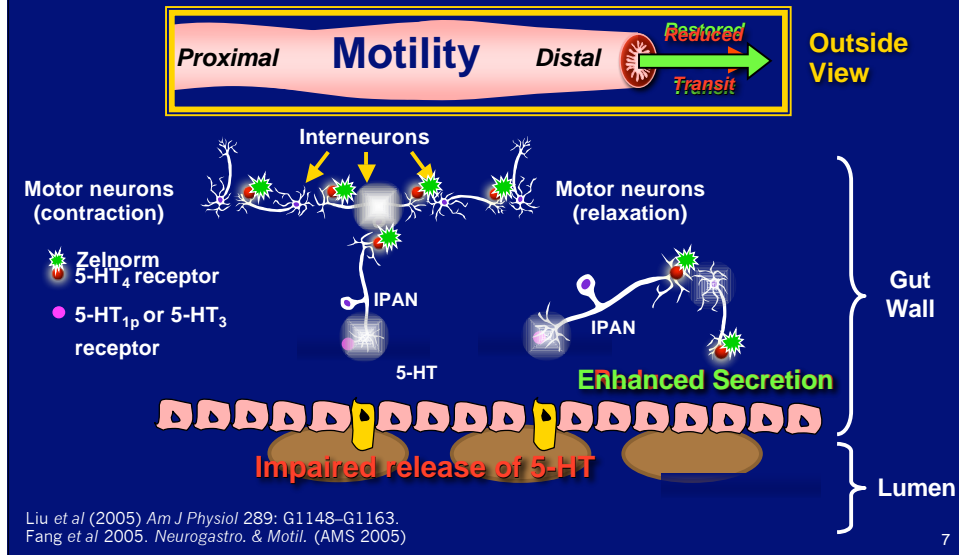


Camilleri, Aliment Pharmacol Ther 2001; 15: 277

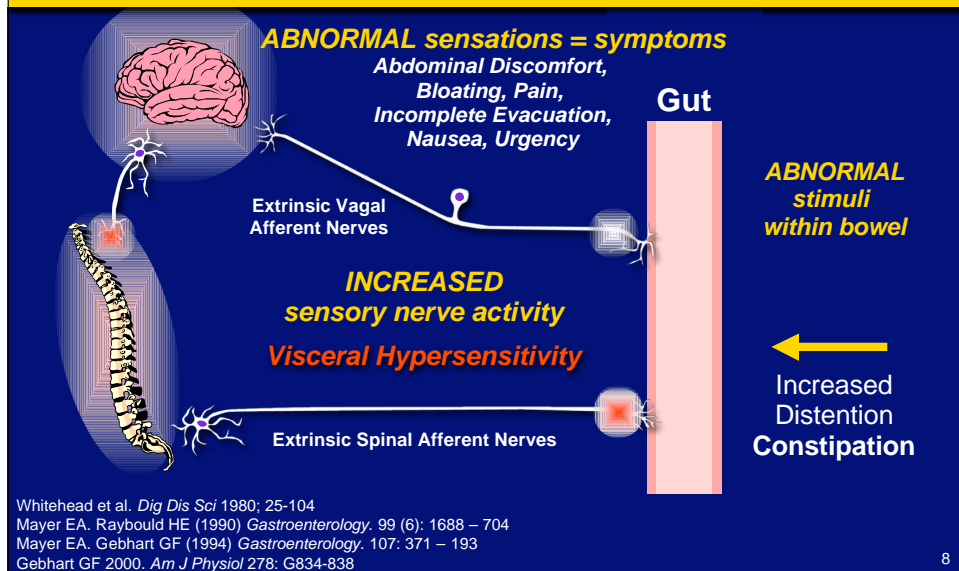
Impaired 5HT-Release Leads to Impaired Enteric Reflexes, Dysmotility, and Reduced Secretion



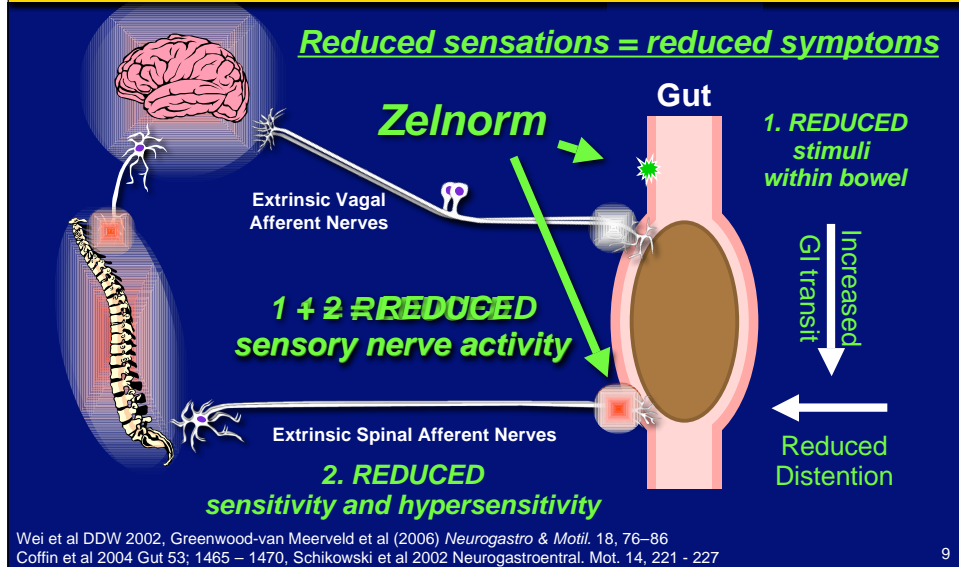
Zelnorm Amplifies Enteric Reflexes Resulting in Increased Motility and Secretion



Constipation, and Visceral Hypersensitivity, lead to Increased Sensory Signaling to CNS



Zelnorm Reduces Sensory Symptoms by Reducing Distention & by Inhibiting Sensory Nerves



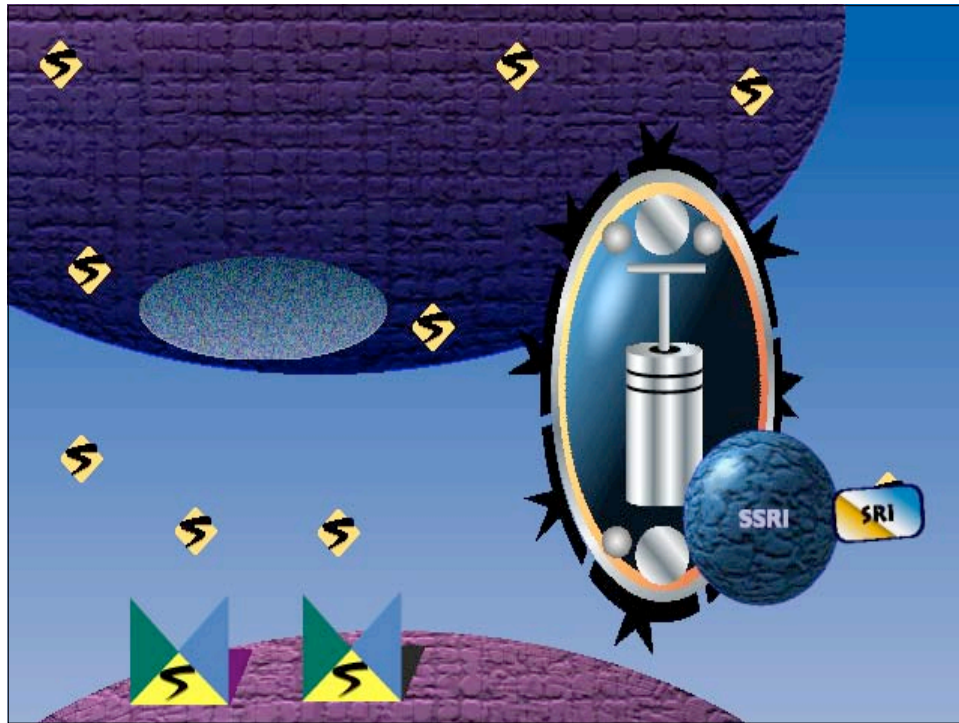
Effect of tegaserod on additional dysmotility symptoms of IBS-C¹

- ↑ 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

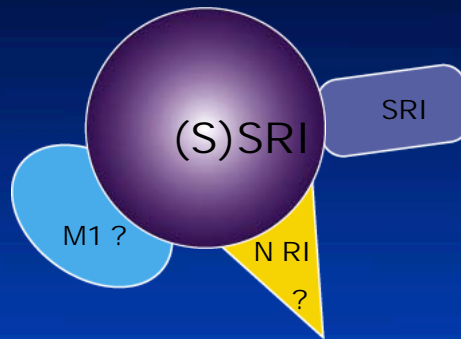
Citalopram (Celexa) 20-60 mg

Sertraline (Zoloft) 50-250 mg

Paroxetine (Paxil) 20-80 mg

Fluoxetine (Prozac) 20-80 mg

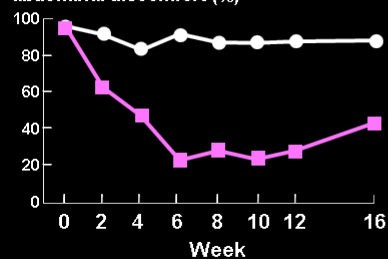
Fluvoxamine (Luvox) 100-300 mg



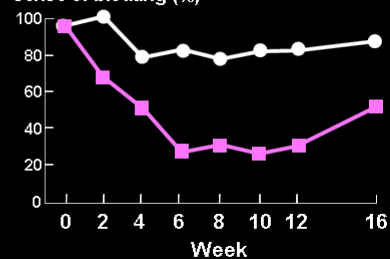
Therapeutic effects of fluoxetine in IBS-C patients: A randomized-controlled study

Treatment period was 12 weeks

Subjects with significant abdominal discomfort (%)



Subjects with significant sense of bloating (%)



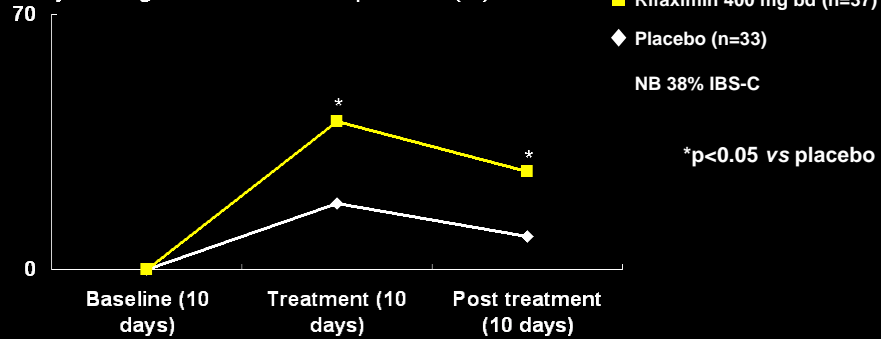
—●— Placebo (n=22) —■— Fluoxetine 20 mg daily (n=22)

- 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

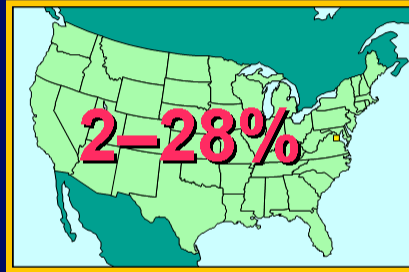
IDIOPATHIC



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

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 | + | +++ |

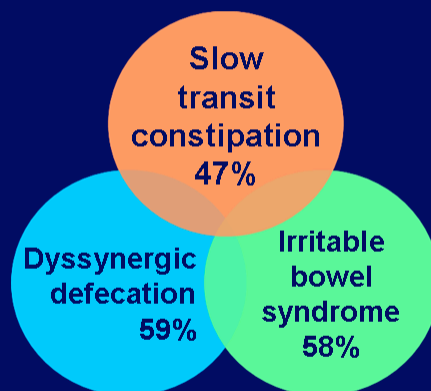
CC and IBS-C lie along a spectrum of abdominal discomfort and pain



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.

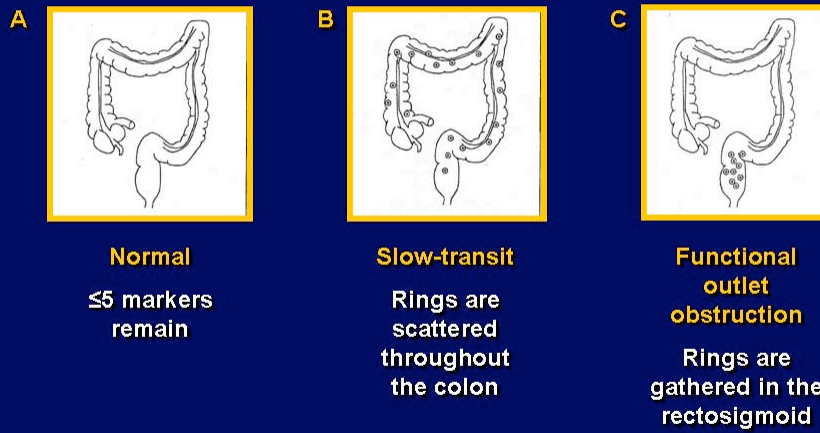
Functional subtypes of idiopathic constipation



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

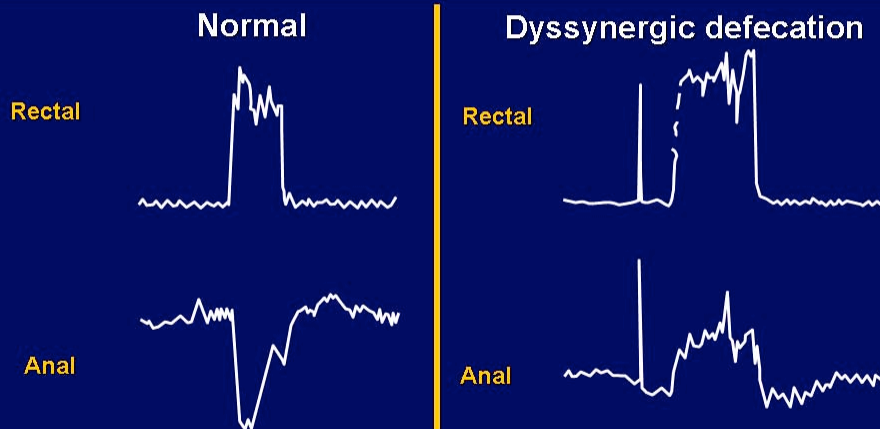
Rao et al, *Gastroenterol Clin North Am* 2003; 32: 659
Mertz et al, *Am J Gastroenterol* 1999; 94: 609

Measurement of colonic transit: Distribution of radiographic markers



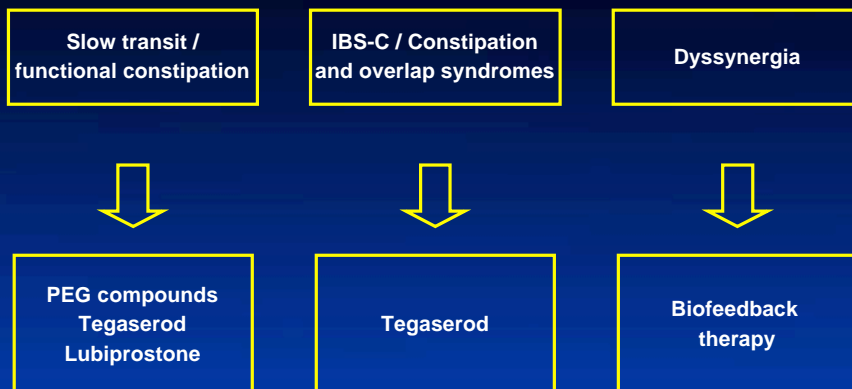
Faigel et al, Clin Cornerstone 2002; 4: 11

Manometry in patients with dyssynergia

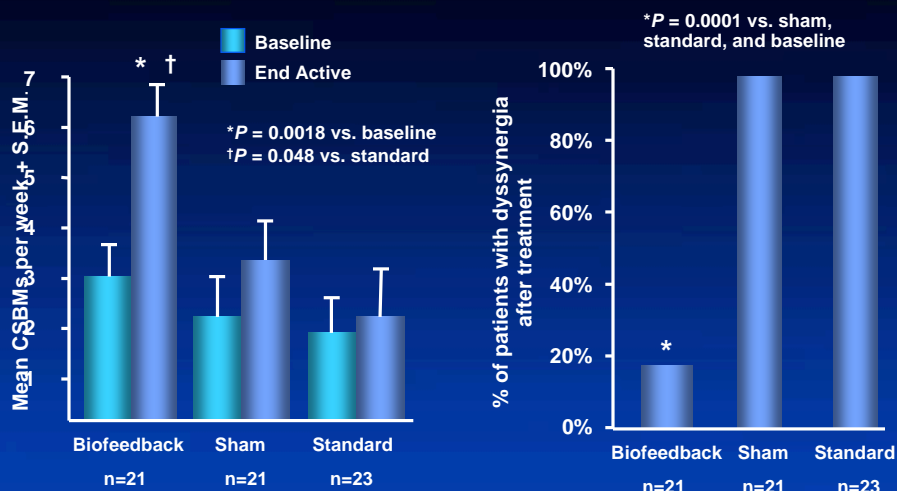


Rao, Gastroenterol Clin North Am 2003; 32: 659

Pathophysiologic-based treatment approach for chronic constipation

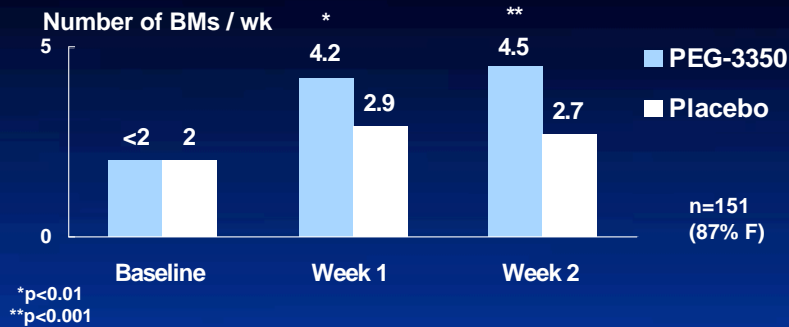


Biofeedback Therapy for Dyssynergic Constipation (Randomized Controlled Trial)



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

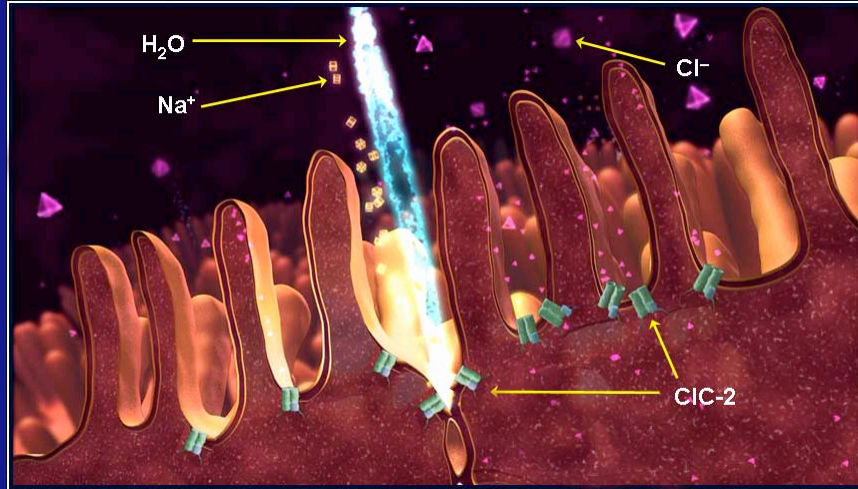
Summary: Tegaserod in chronic constipation

In chronic constipation, tegaserod:

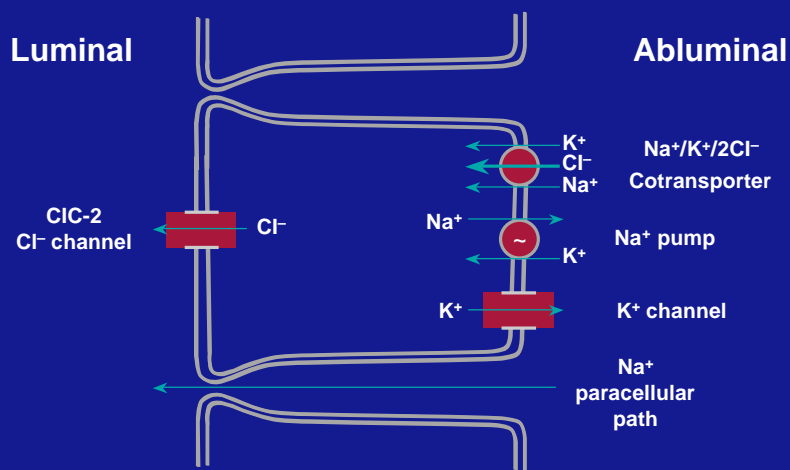
- Normalizes impaired motility and stimulates intestinal secretion
- Increases bowel movements
- Provides effective and sustained relief of:
 - straining
 - hard / lumpy stools
- Improves global constipation relief score
- Has a favorable safety profile

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

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

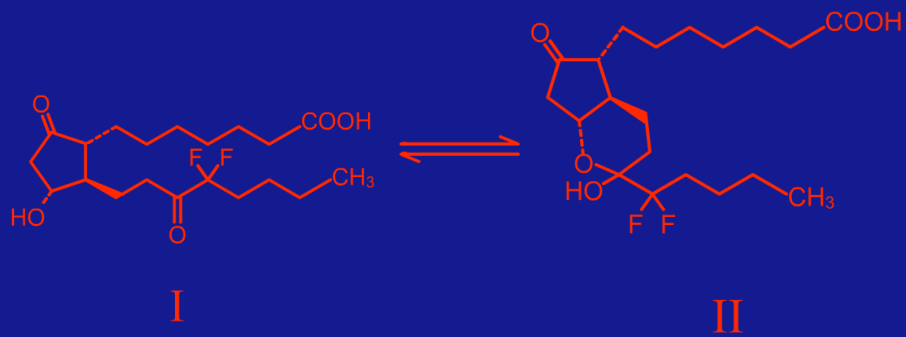


Intestinal Expression of CIC-2 Chloride Channels

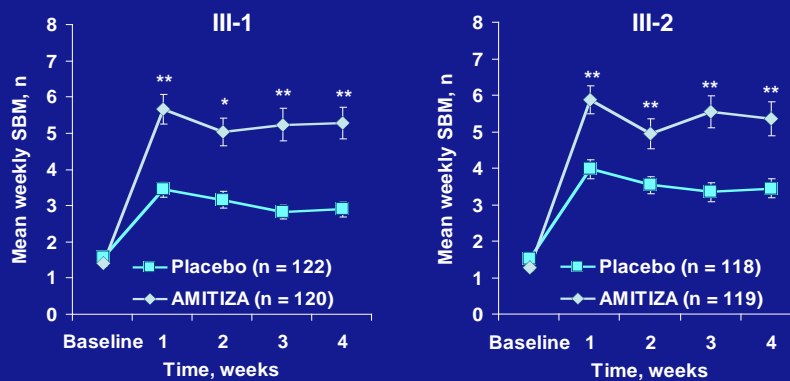


Adapted from Cuppoletti J, et al. *Am J Physiol Cell Physiol.* 2004;287:C1173-C1183.

AMITIZA™ (lubiprostone) Is a Bicyclic Fatty Acid



AMITIZA™ (lubiprostone) Increased Weekly Spontaneous Bowel Movements



AMITIZA significantly increased SBM over baseline and placebo by week 1

SBM = Spontaneous bowel movements.
* $P < .01$, ** $P < .001$, AMITIZA 48 mcg versus placebo.

AMITIZA™ (lubiprostone) Activates ClC-2 Chloride Channels

- Specific chloride channel-2 (ClC-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 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%) |

[†]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%)

¹Lubiprostone PI

²Tegaserod PI

³Johanson, *Am J Gastroenterol* 2005; 100: S324

⁴Kamm, *Am J Gastroenterol* 2005; 100: 362

FDA-approved prescription medications for constipation

