

Irritable Bowel Syndrome and Chronic Constipation

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Treatment of IBS

Abdominal pain / discomfort

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

Constipation

- Fiber
- MOM/PEG solution
- Tegaserod

Abdominal
pain /
discomfort

Bloating /
distention

Altered bowel
function

Bloating

- Tegaserod
- Dietary changes
- ? Probiotics
- ? Antibiotics

Diarrhea

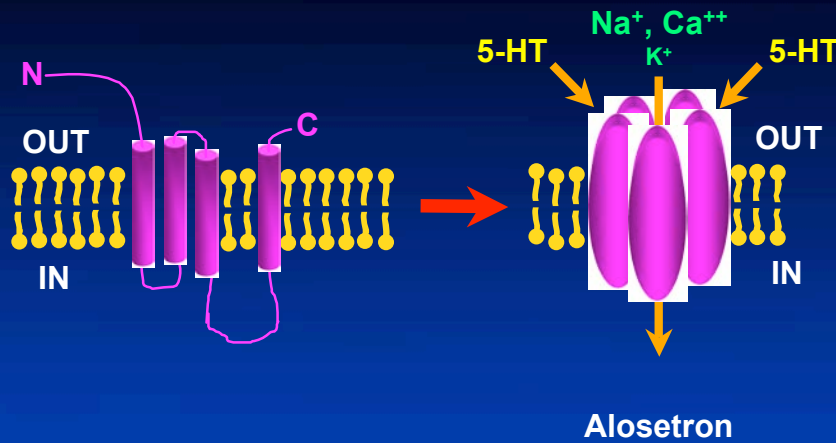
- Loperamide
- Other opioids
- Alosetron



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.

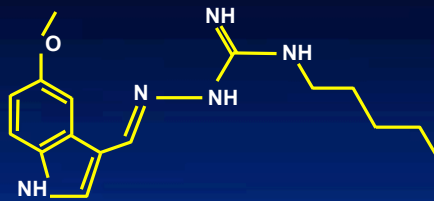
Mechanisms of Action of 5-HT₃ receptor antagonists

- 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

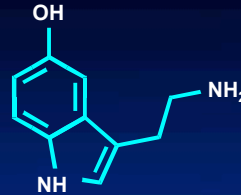


1. Kim D-Y, Camilleri M. *Am J Gastroenterol.* 2000;95:2698–2709.
2. Viramontes BE et al. *Am J Gastroenterol.* 2001;96:2671–2676.

Tegaserod (Zelnorm) 2002



Tegaserod



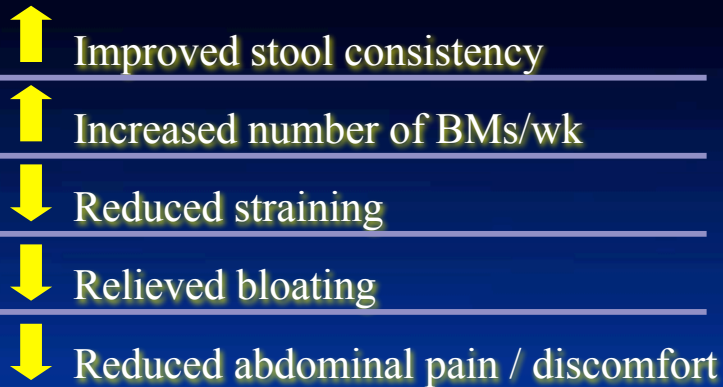
Serotonin (5-HT)

- Tegaserod is a 5-HT₄ receptor agonist
- new class of compound: aminoguanidine indoles
- Structure similar to serotonin
- Suspended from market March 2007



Camilleri, Aliment Pharmacol Ther 2001; 15: 277

Effect of tegaserod on additional
dysmotility symptoms of IBS-C¹

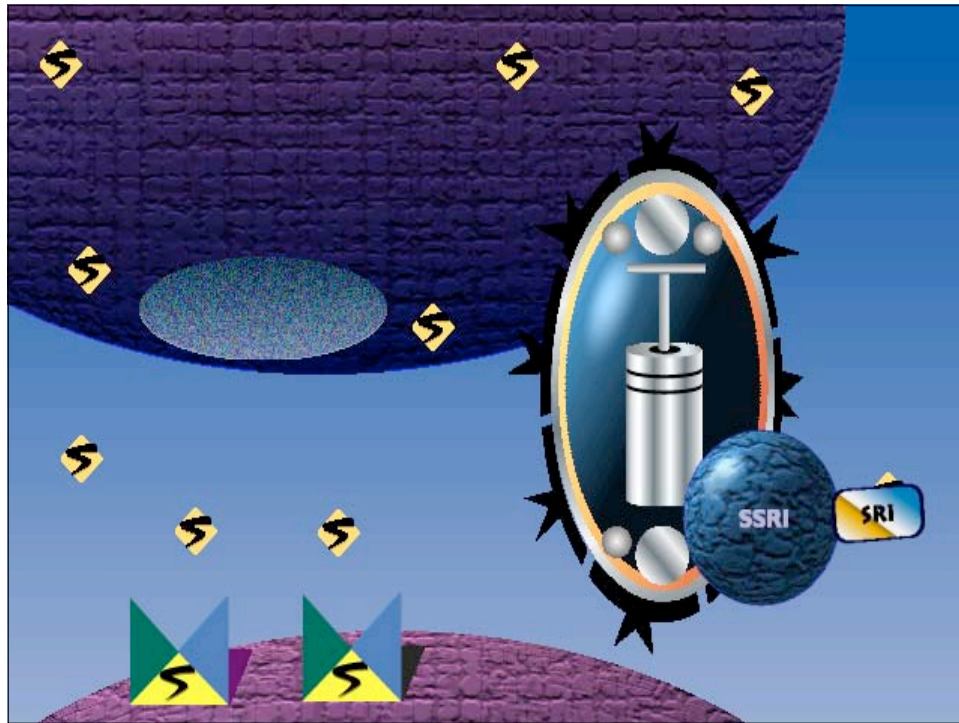


- In a double-blind RCT (tegaserod n=1645; placebo n=405): IBS-C QoL was significantly better in patients treated with tegaserod, p=0.005 vs placebo²
- Efficacy beyond 12 weeks has not been studied
- Response rates vs placebo were greater at month 1 than at month 3



¹Kellow et al, *Gut* 2003; 52: 671

²Patrick et al, *Gastroenterol* 2005; 128: A287

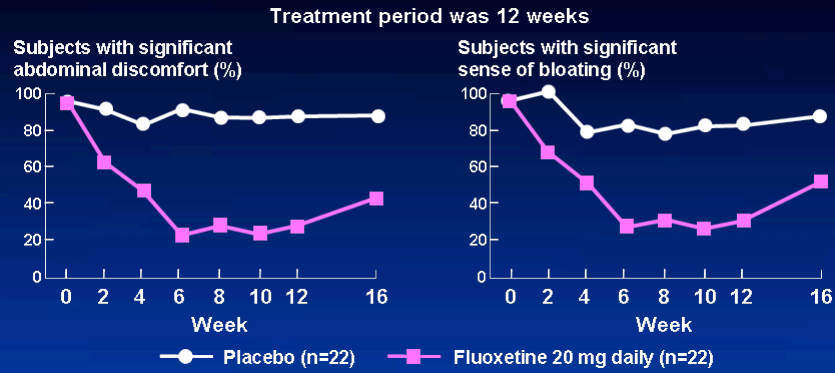


Serotonin Transporter (SERT)

- 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





- 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

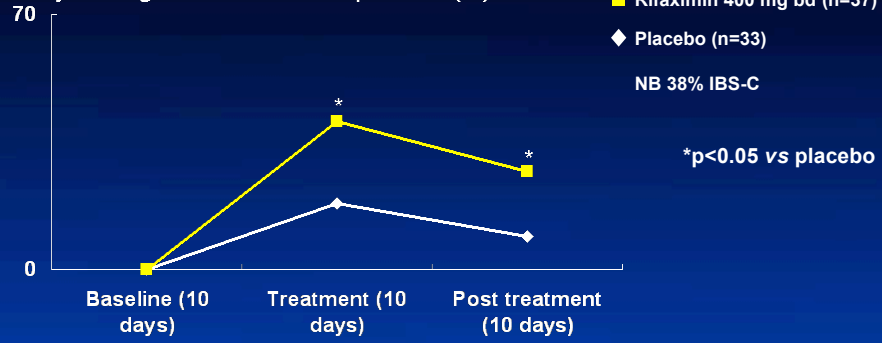
Vahedi et al, *Aliment Pharmacol Ther* 2005; 22: 381

Rifaximin + IBS

- RCT (n=87, P=44, R=43)
 - 2 Centers: n=84, n=3
- Rome I Criteria for IBS
- Rifaximin: 400 mg PO TID x 10 days
 - Follow up: 10 weeks
- Results:
 - Greater improvement in global IBS Sxs with Rifax
 - Lower bloating score after Rifax

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

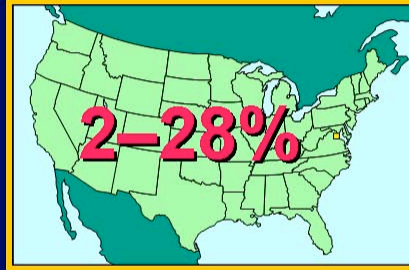
CHRONIC
IDIOPATHIC
CONSTIPATION



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

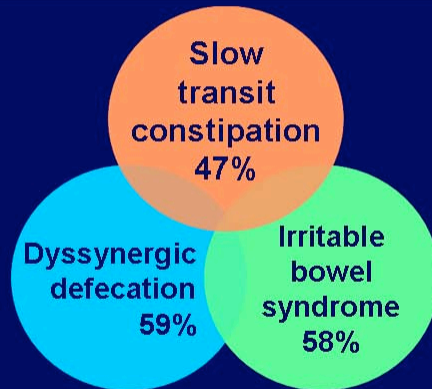


IBS-C = irritable bowel syndrome with constipation.

Thompson WG et al. *Gut*. 1999;45(suppl 2):II43-II47.

Drossman DA et al. *Gastroenterology*. 1997;112:2120-2137.

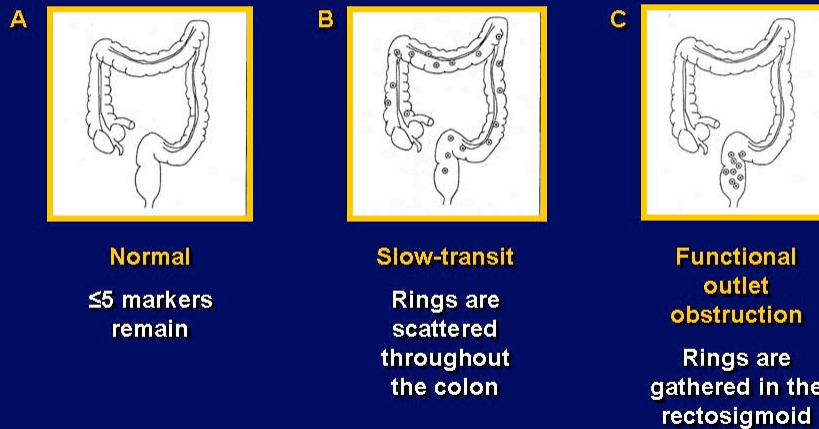
Functional subtypes of idiopathic constipation



- 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



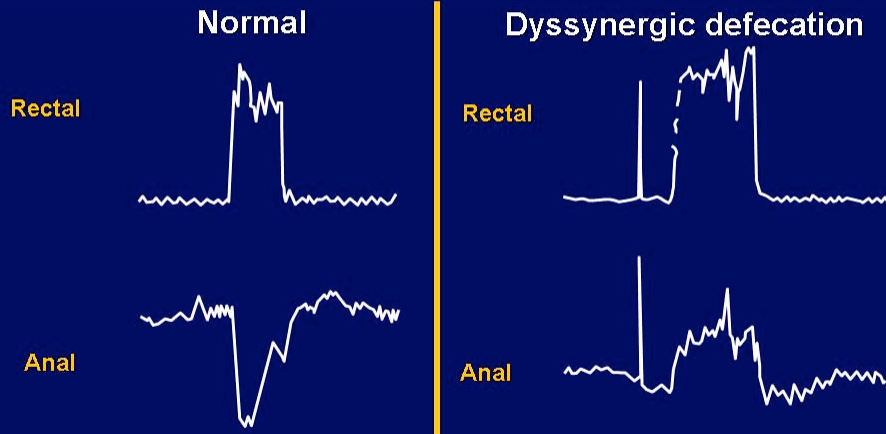
A Normal
 ≤ 5 markers remain

B Slow-transit
 Rings are scattered throughout the colon

C Functional outlet obstruction
 Rings are gathered in the rectosigmoid

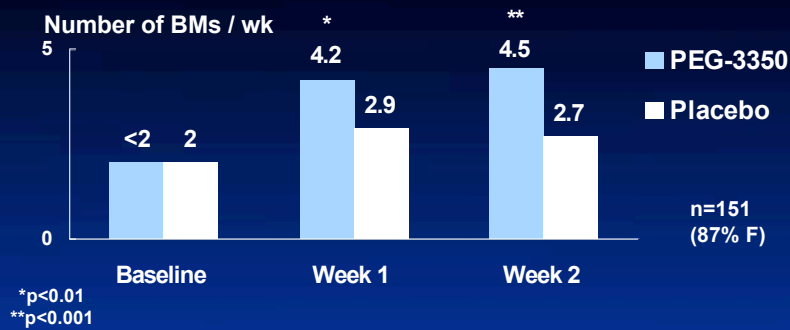
Faigel et al, Clin Cornerstone 2002; 4: 11

Manometry in patients with dyssynergia



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

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

Tegaserod

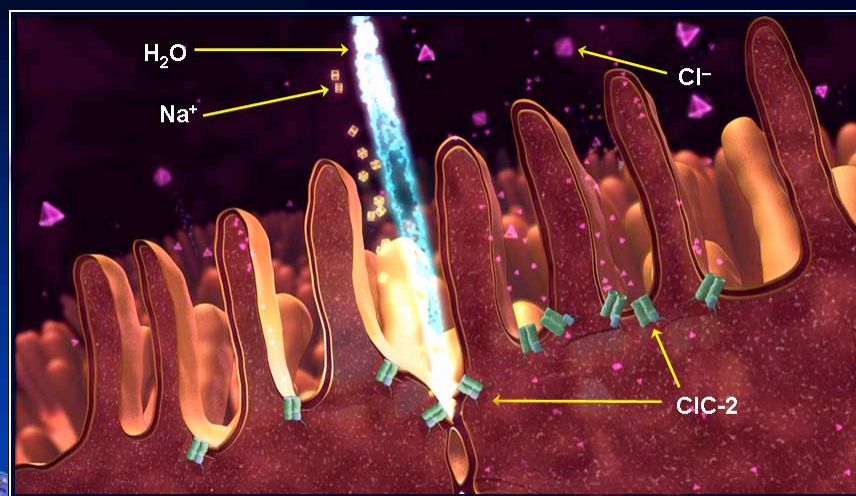
- normalizes motility + stimulates intestinal secretion
- increases bowel movements
- provides relief of straining + hard/lumpy stools
- Improves global constipation relief score
- Suspended from market 3/2007, concern re: ischemic events

Johanson et al, Gastroenterol 2003; 124 (suppl 1)

Talley et al. Am J Gastroenterol 2003; 98(9): S269



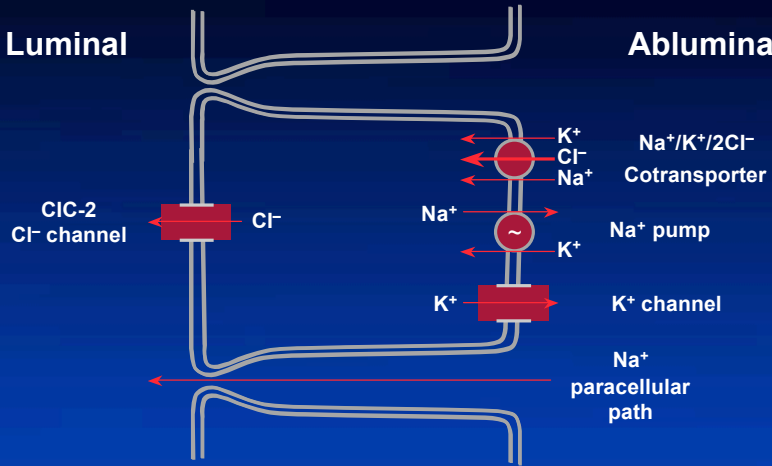
AMITIZA™ (lubiprostone) Activates Intestinal ClC-2 Chloride Channels



Intestinal Expression of
ClC-2 Chloride Channels

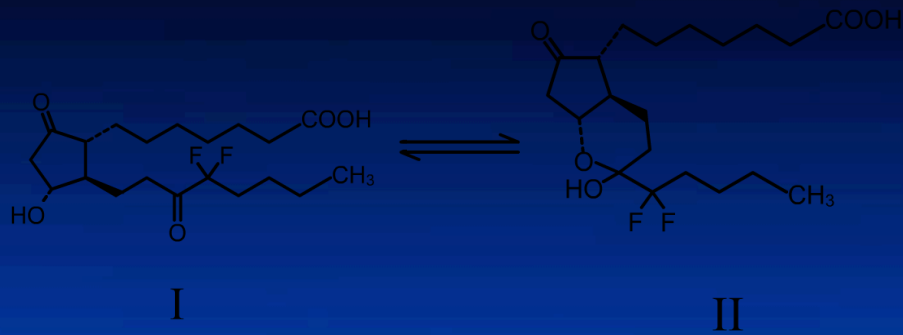
Luminal

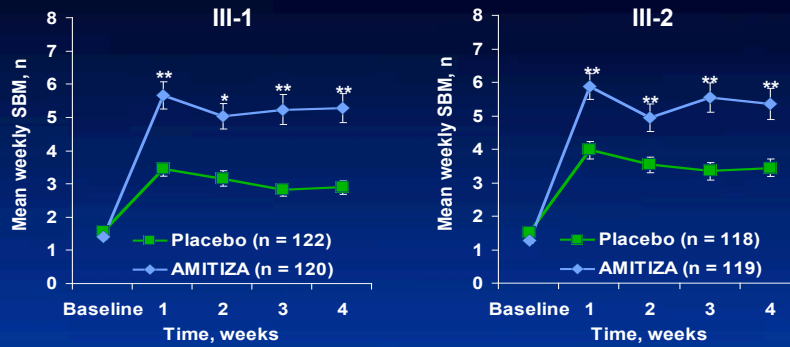
Abluminal



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

AMITIZA™ (lubiprostone) Is a Bicyclic Fatty Acid





AMITIZA significantly increased SBM over baseline and placebo by week 1

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

- 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

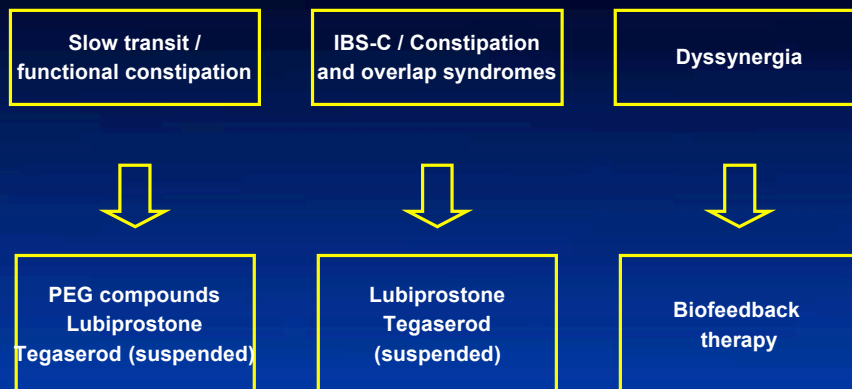
	Lubiprostone ¹	Tegaserod ² (Suspended)
Description	Chloride channel activator	5-HT ₄ agonist
Mechanism of action	Increases intestinal fluid secretion	Stimulates the peristaltic reflex Stimulates intestinal secretion Inhibits visceral sensitivity
Indications	CC in male and female patients	CC in male and 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%)

[†]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

Pathophysiologic-based treatment approach for chronic constipation



What is IBS?

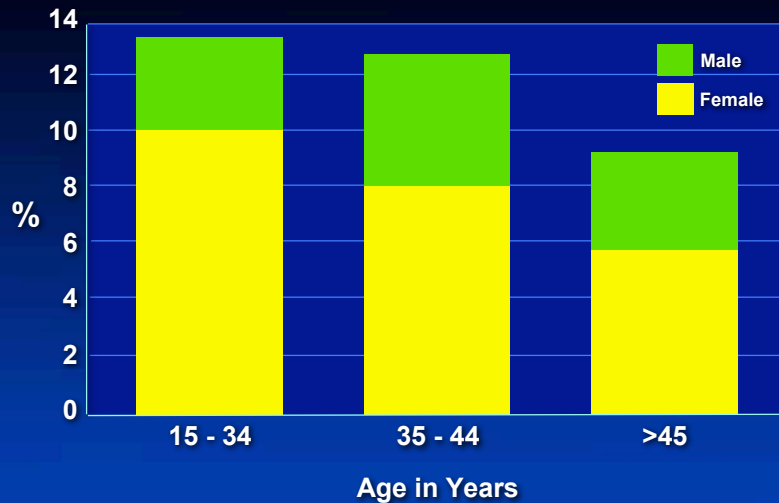
- a chronic, intermittent gastrointestinal condition
- a **FUNCTIONAL** bowel disorder without evidence of structural or biochemical abnormalities
- characterized by **ABDOMINAL PAIN or DISCOMFORT** associated with altered bowel function:
 - diarrhea
 - constipation
 - bloating or feeling of distension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



Drossman et al, Gastroenterology 1997; 112: 2120

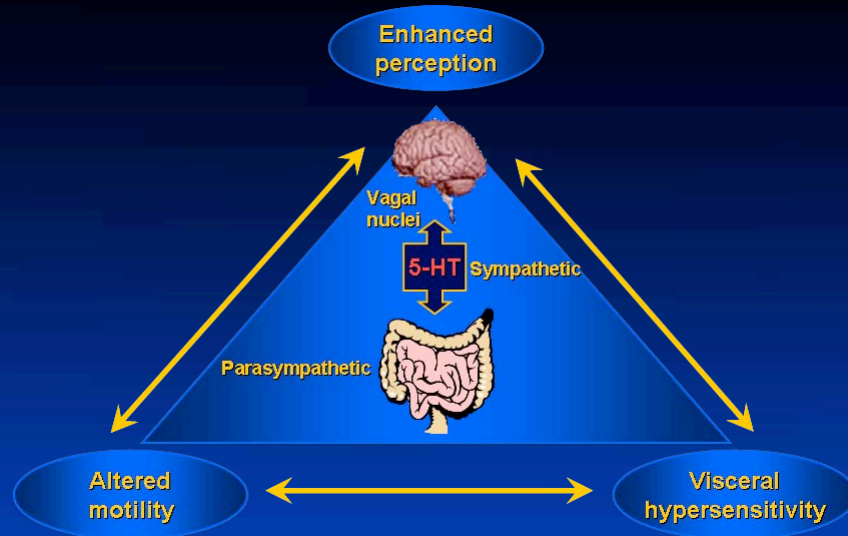
IBS - Epidemiology

U.S. Prevalence



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

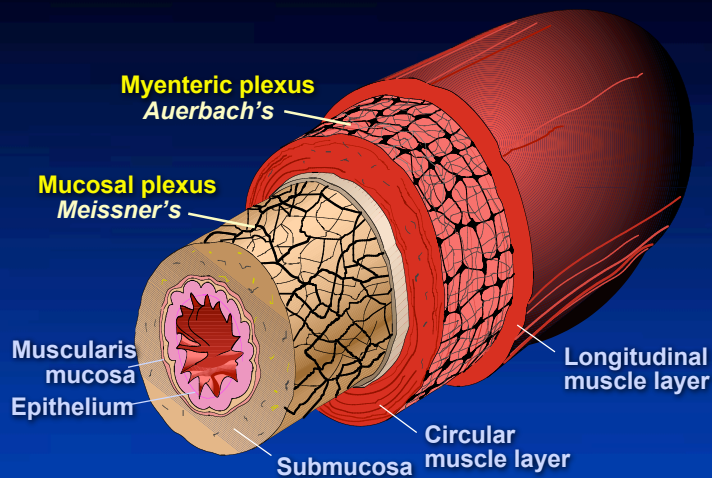
Brain-gut connection in IBS



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

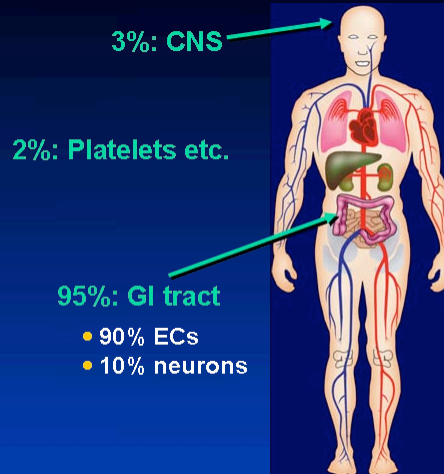
IBS - Pathophysiology

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:

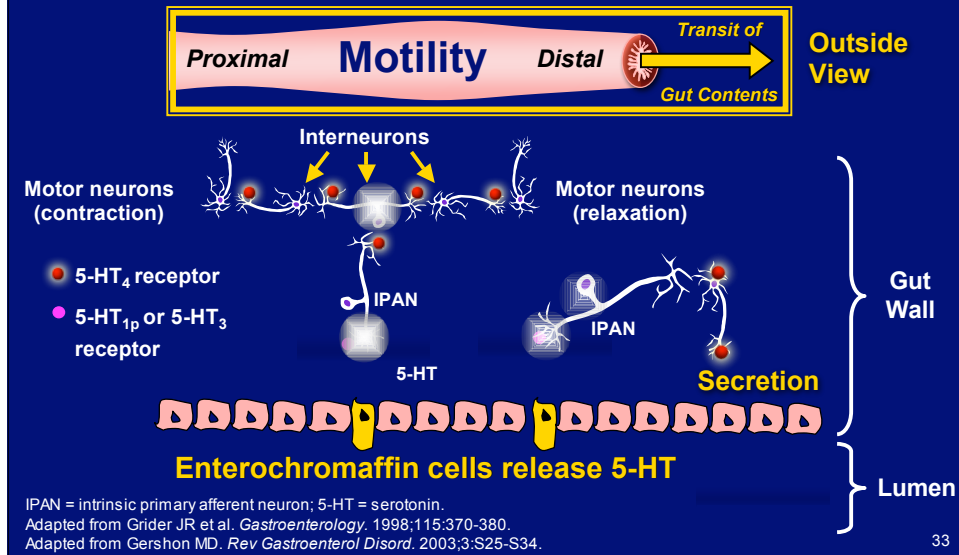
- Serotonin
- Acetylcholine
- Nitric oxide
- Substance P
- Vasoactive intestinal peptide
- Cholecystikinin

Visceral sensitivity:

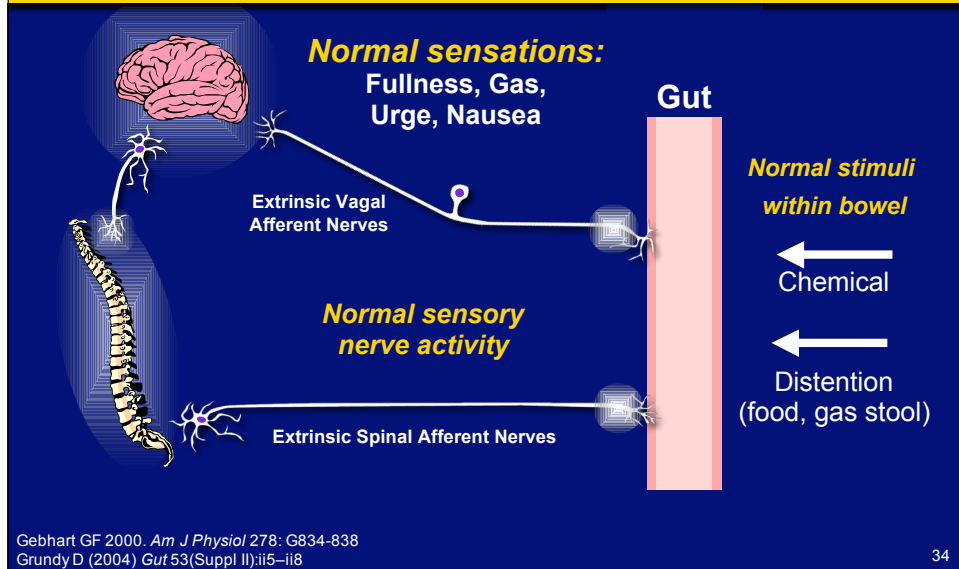
- Serotonin
- Tachykinins
- Calcitonin gene-related peptide
- Neurokinin A
- Enkephalins

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

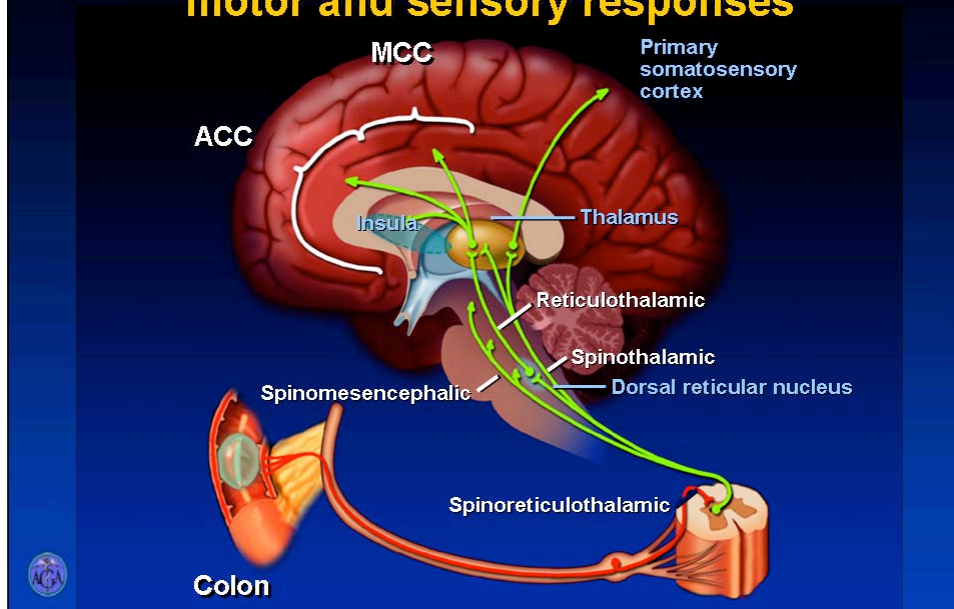
Serotonin Release Stimulates Motility and Secretion via Enteric Nerve Reflexes



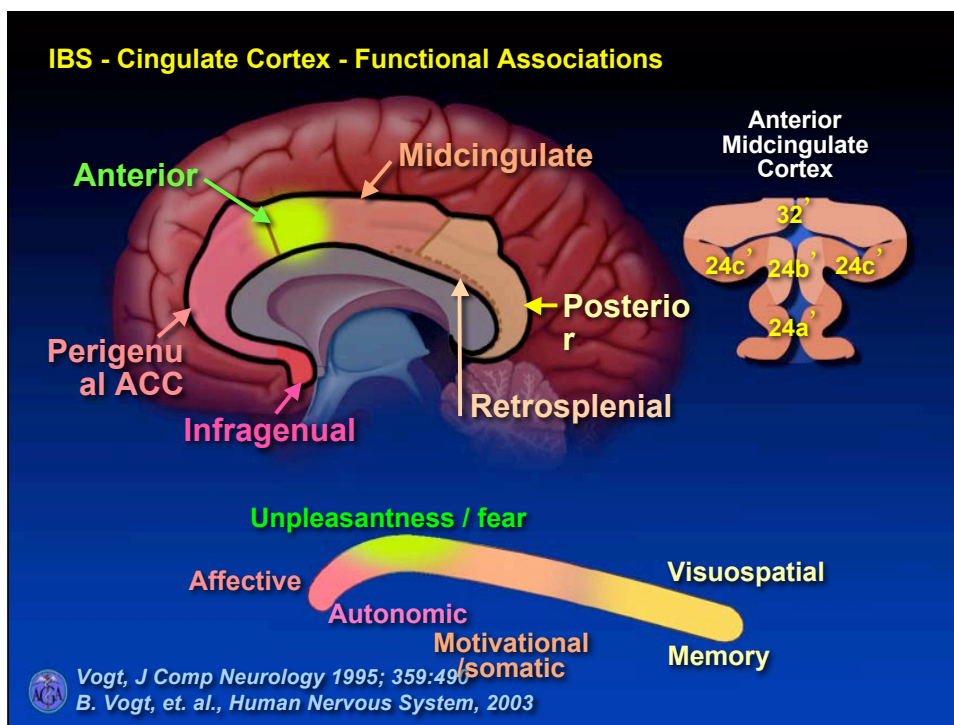
Normal Signals, Transmitted by Normal Sensory Nerves lead to Normal Sensations

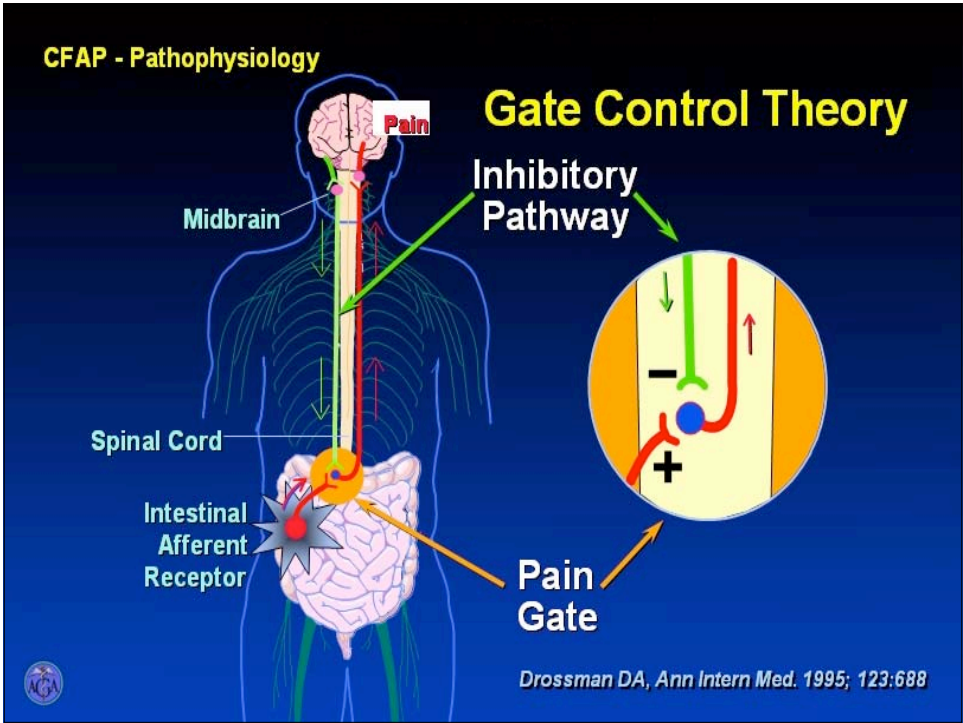
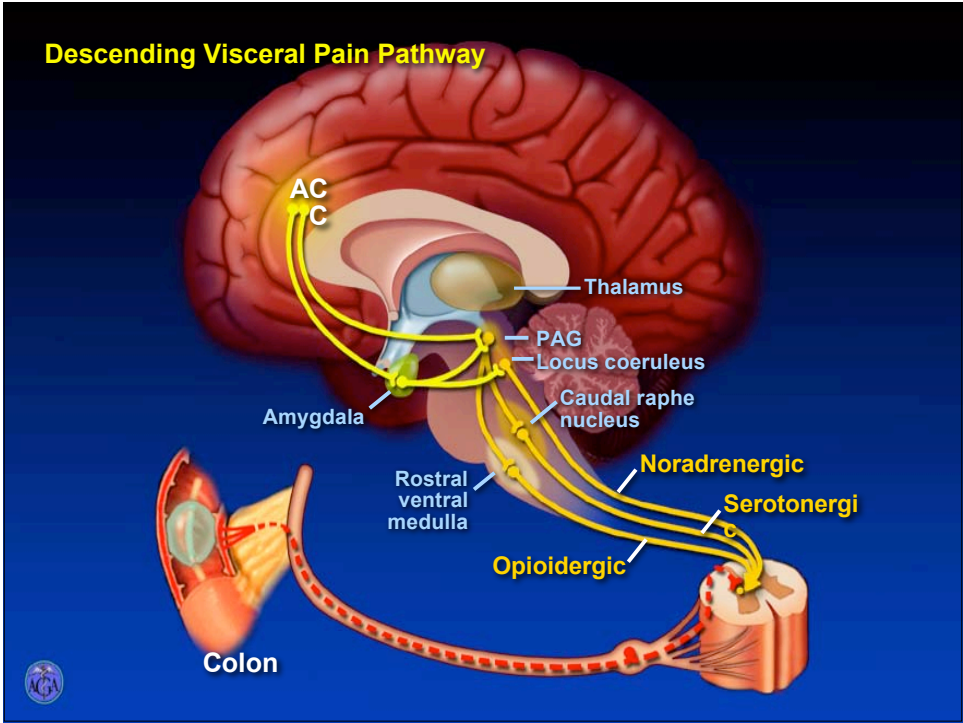


Brain-gut interactions modulating visceral motor and sensory responses



IBS - Cingulate Cortex - Functional Associations





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

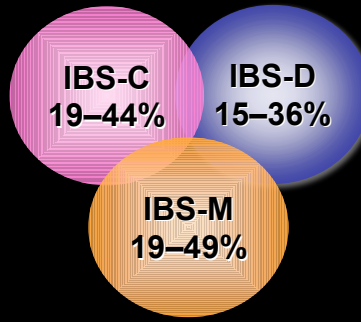
Longstreth et al, Gastroenterology 2006; 130:1480

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