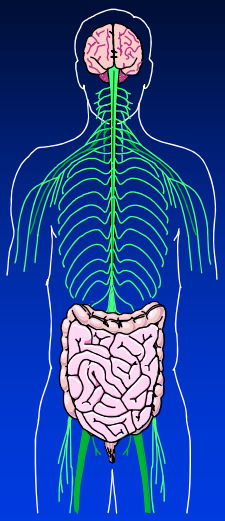
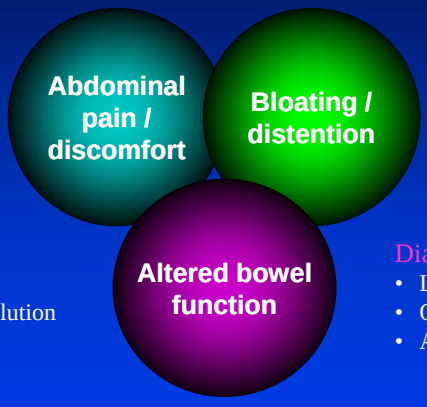


Irritable Bowel Syndrome and Chronic Constipation

Susan Lucak, M.D.
Columbia University Medical Center

Treatment of IBS

Abdominal pain / discomfort
- Antispasmodics
- Antidepressants
  - TCAs / SSRIs
- Alosetron
- Tegaserod



Bloating
- Tegaserod
- Dietary changes
- ? Probiotics
- ? Antibiotics

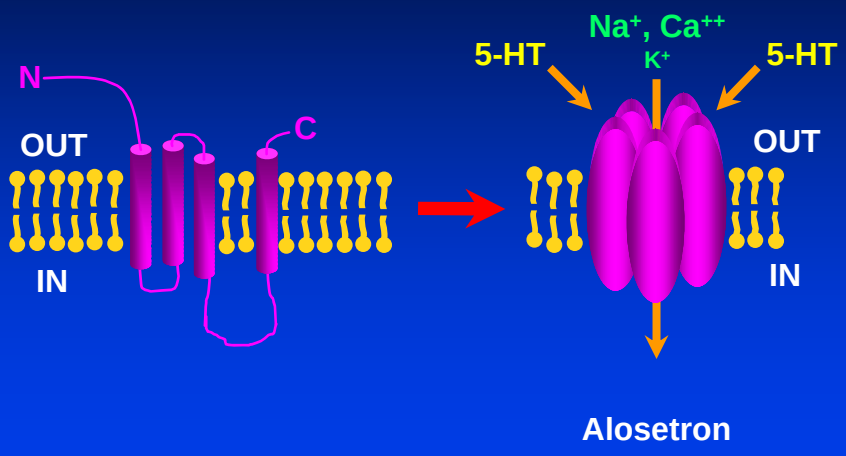
Constipation
- Fiber
- MOM/PEG solution
- Tegaserod

Diarrhea
- Loperamide
- Other opioids
- Alosetron

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

Alosetron (Lotronex) 2000

5-HT$_3$ Antagonist: Mechanisms of Action



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

Mechanisms of Action of 5-HT 3 receptor antagonists

- Delay small bowel and colonic transit[1,2]
  - treat diarrhea
- Increase colonic compliance[1]
  - improve fecal urgency
- Inhibit chloride secretion[1]
  - make stools more formed
- Blunt the gastrocolonic response[1]
  - improve urgency
- Affect visceral afferent[1]
  - 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-HT$_4$ receptor agonist**
- **new class of compound: aminoguanidine indoles**
- **Structure similar to serotonin**
- **Suspended from market March 2007**

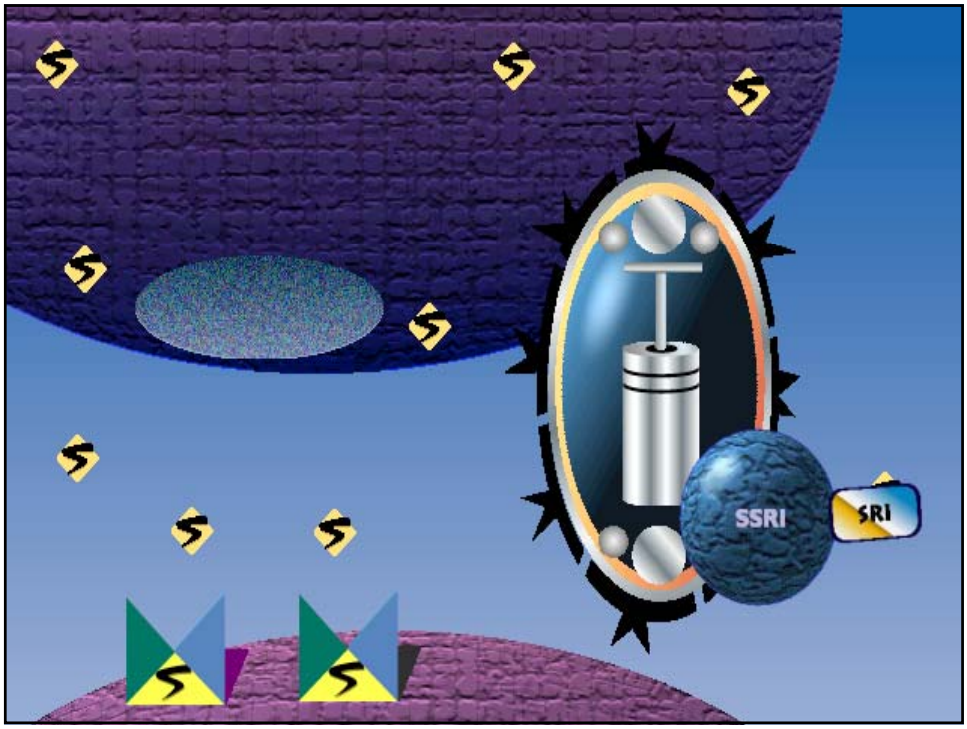
Camilleri, Aliment Pharmacol Ther 2001; 15: 277

Effect of tegaserod on additional dysmotility symptoms of IBS-C[1]

- 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[2]
- Efficacy beyond 12 weeks has not been studied
- Suggests some symptoms may respond to agents other than laxatives

[1]Kellow et al, Gut 2003; 52: 671
[2]Patrick et al, Gastroenterol 2005; 128: A287

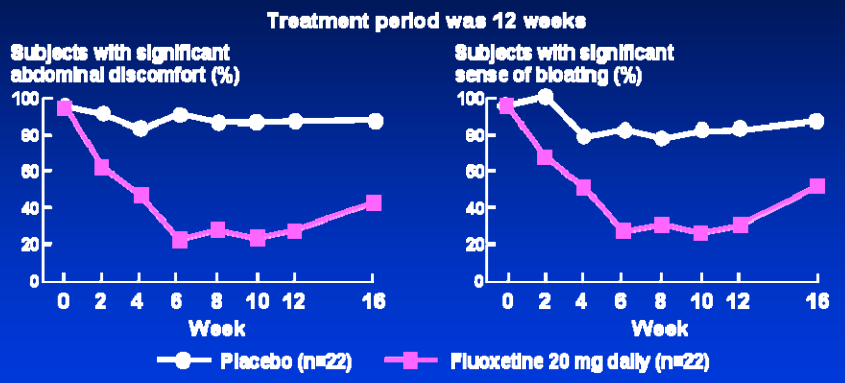


Serotonin Transporter (SERT)

- 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 Nuerosci 1996; 16:2352-64

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



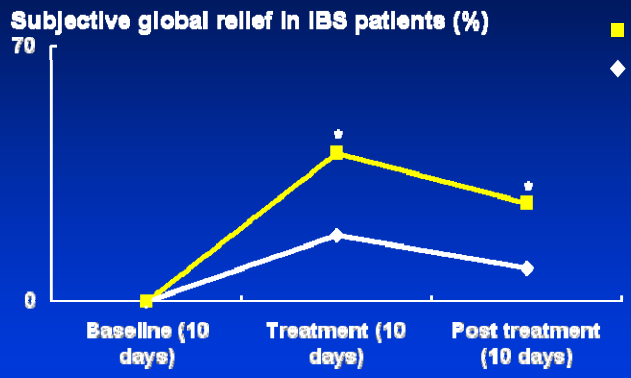
- At week 4, all symptoms evaluated (bloating, discomfort, stool consistency, change in bowel habit <3 bowel movements / week) less frequent in the fluoxetine patients *vs* placebo ($p<0.05$)
- Mean number symptoms per patient decreased from 4.6–0.7 in fluoxetine patients *vs* 4.5–2.9 in control patients ($p<0.001$)
- 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



- Rifaximin 400 mg bd (n=37)
- Placeb0 (n=33)

NB 38% IBS-C

*p<0.05 *vs* placebo

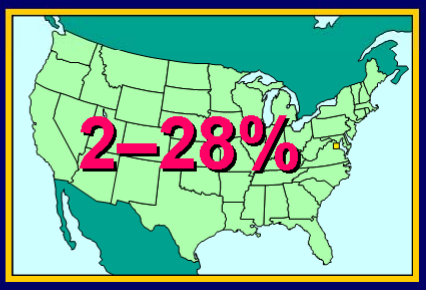
- Antibiotic
- Modest effect in short term management of gas-related abdominal symptoms
- Study limitations: short duration of treatment and follow-up, small sample size

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-years[4]



[1]Locke et al, Gastroenterology 2000; 119: 1766
[2]Stewart et al, Am J Gastroenterol 1999; 94(12): 3530
[3]Talley et al, Am J Gastroenterol 1996; 91: 19
[4]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

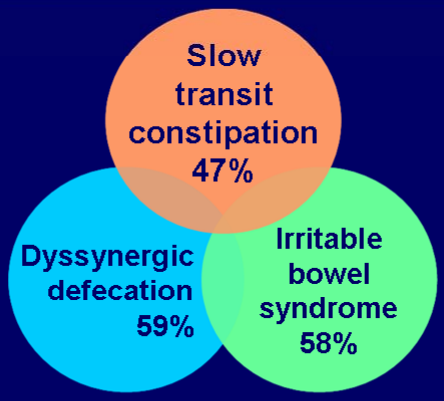
– ← **Abdominal Discomfort** → +

Chronic Constipation — **IBS-C**

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.

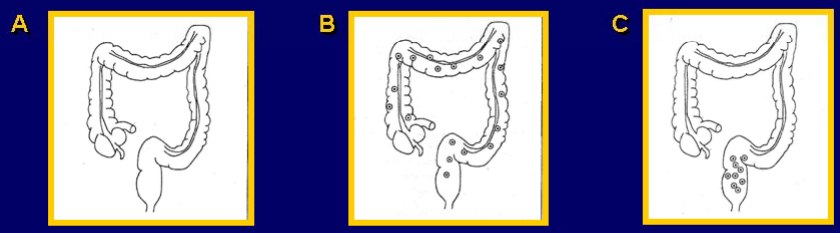
Functional subtypes of idiopathic constipation



- 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



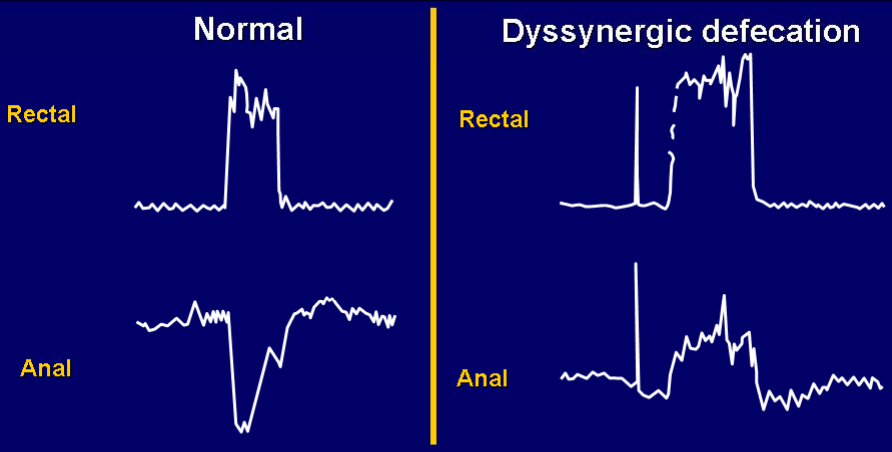
Normal
≤5 markers remain

Slow-transit
Rings are scattered throughout the colon

Functional outlet obstruction
Rings are gathered in the rectosigmoid

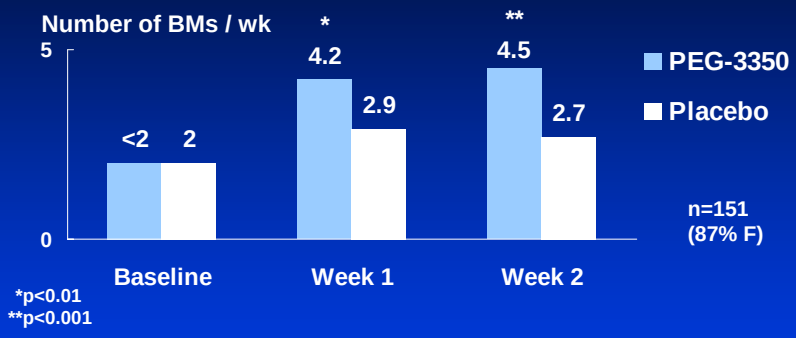
Faigel et al, Clin Cornerstone 2002; 4: 11

Manometry in patients with dyssynergia



Rao, Gastroenterol Clin North Am 2003; 32: 659

Efficacy of PEG-3350 in constipation



*p<0.01
**p<0.001

- 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

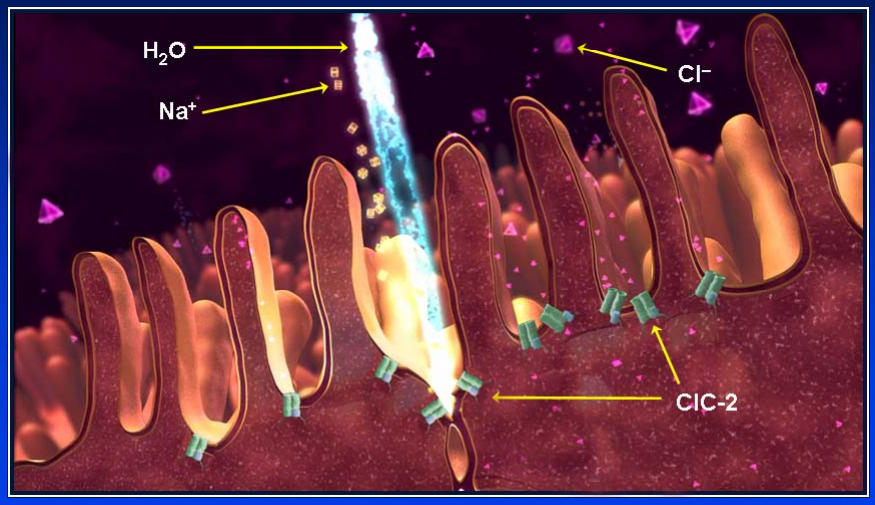
Summary: Tegaserod in Chronic Constipation

Tegaserod

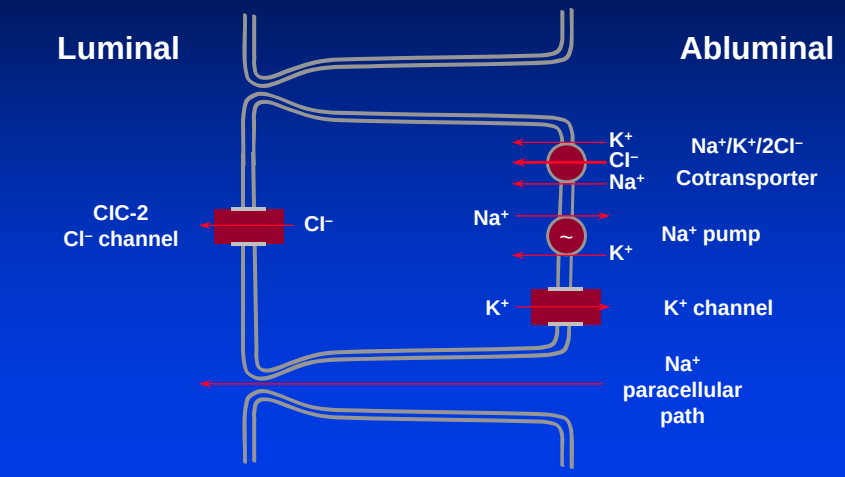
- normalizes motility + stimulates intestinal secretion
- increases bowel movements
- provides relief of straining + hard/lumpy stools
- Improves global constipation relief score
- Suspended from market 3/2007, concern re: ischemic events

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

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

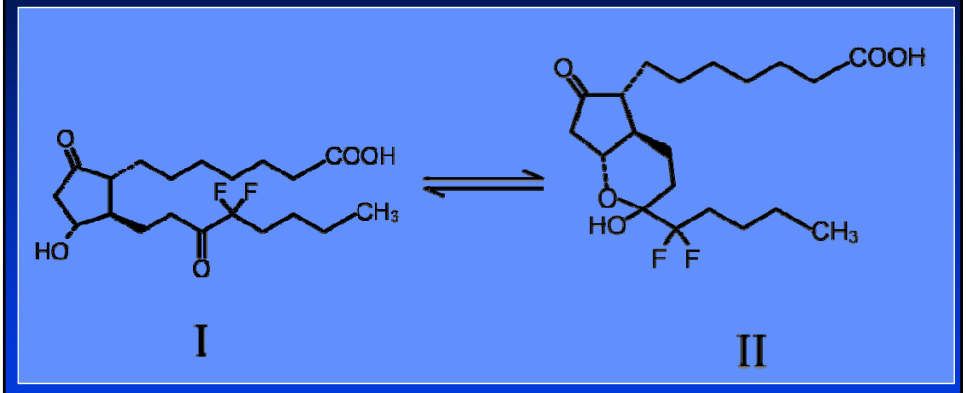


Intestinal Expression of
ClC-2 Chloride Channels

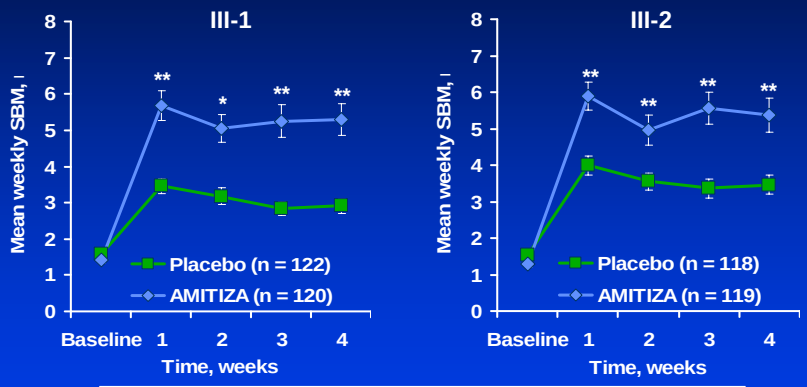


Adapted from Cuppoletti J, et al. *Am J Physiol Cell Physiol*. 2004;287:C1173-C1183.

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.

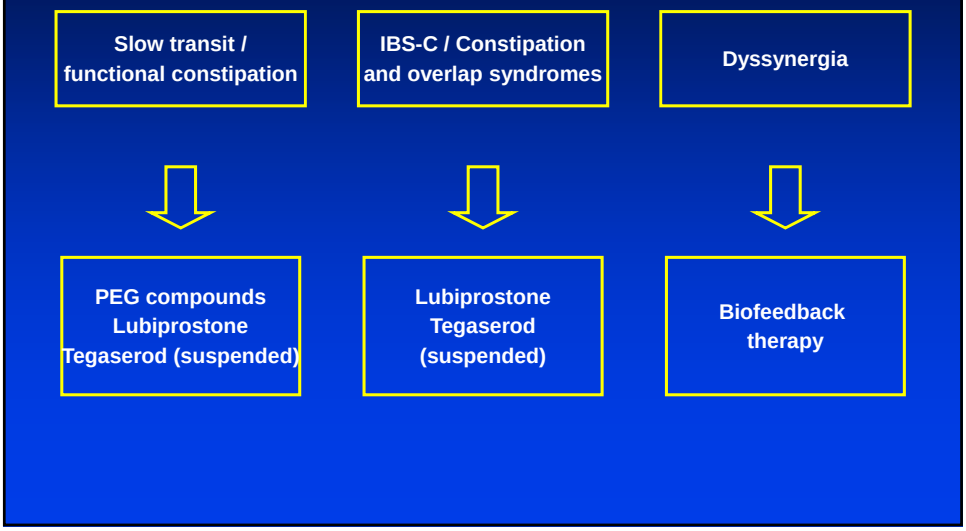
Comparison of lubiprostone and tegaserod in CC

	Lubiprostone[1]	Tegaserod[2] (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%)

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

Pathophysiologic-based treatment approach for chronic constipation



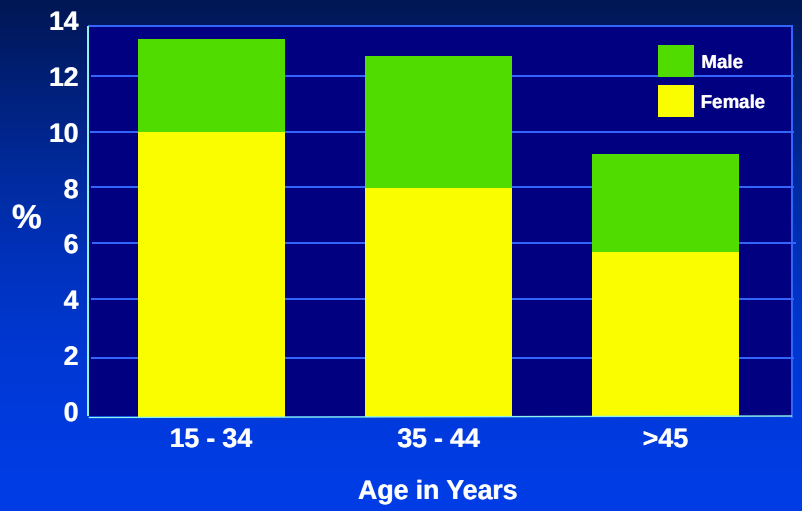
What is IBS?

- 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

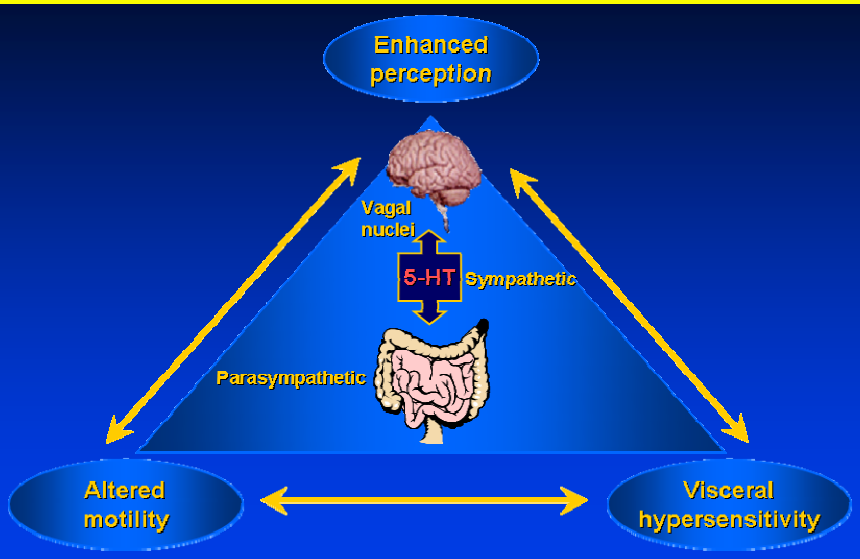
IBS - Epidemiology

U.S. Prevalence



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

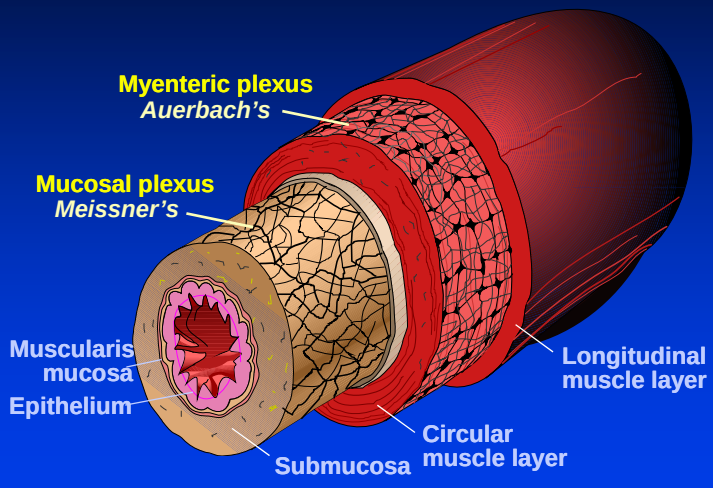
Brain-gut connection in IBS



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

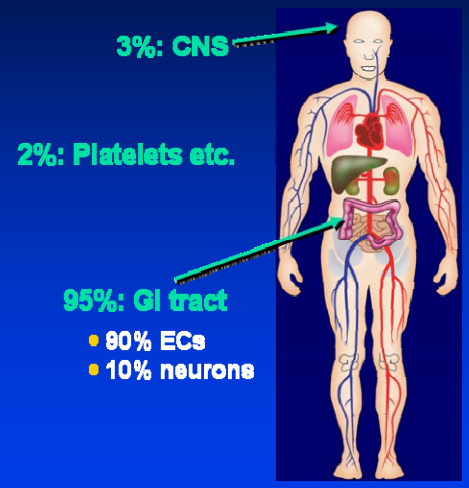
IBS - Pathophysiology

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:

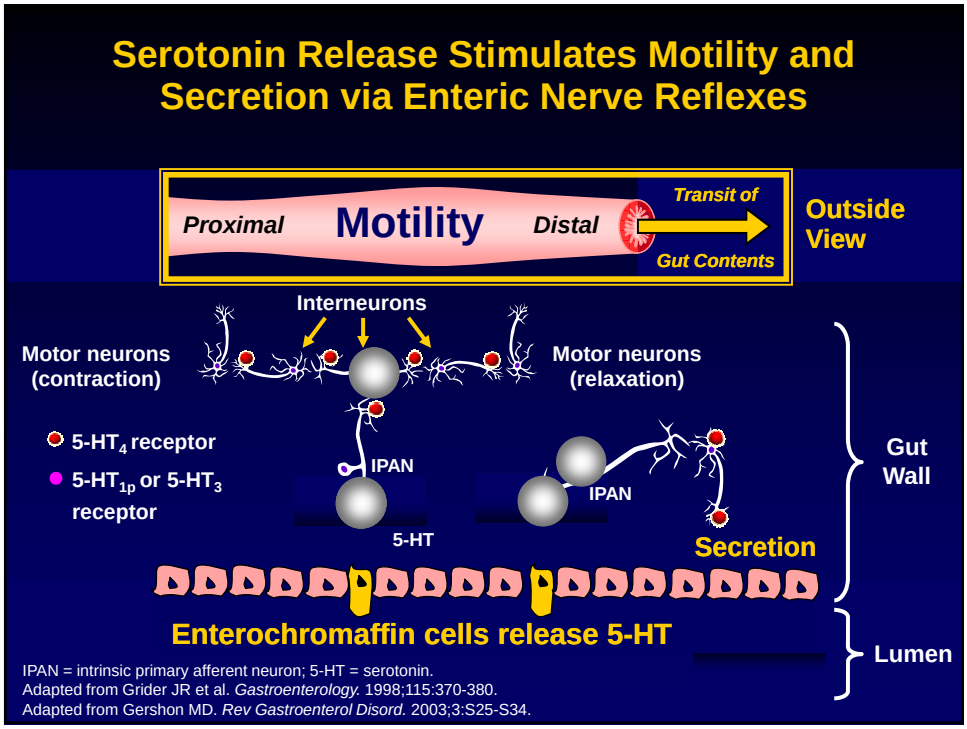
- Serotonin
- Acetylcholine
- Nitric oxide
- Substance P
- Vasoactive intestinal peptide
- Cholecystokinin

Visceral sensitivity:

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

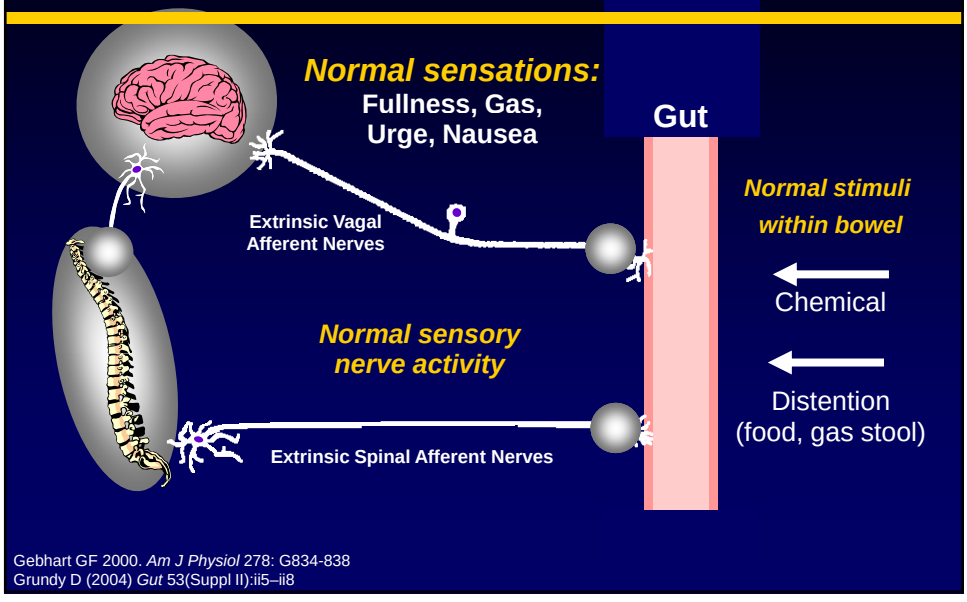
Kim et al, Am J Gastroenterol 2000; 95: 2698
Grider et al, Gastroenterology 1998; 115: 370

Serotonin Release Stimulates Motility and Secretion via Enteric Nerve Reflexes

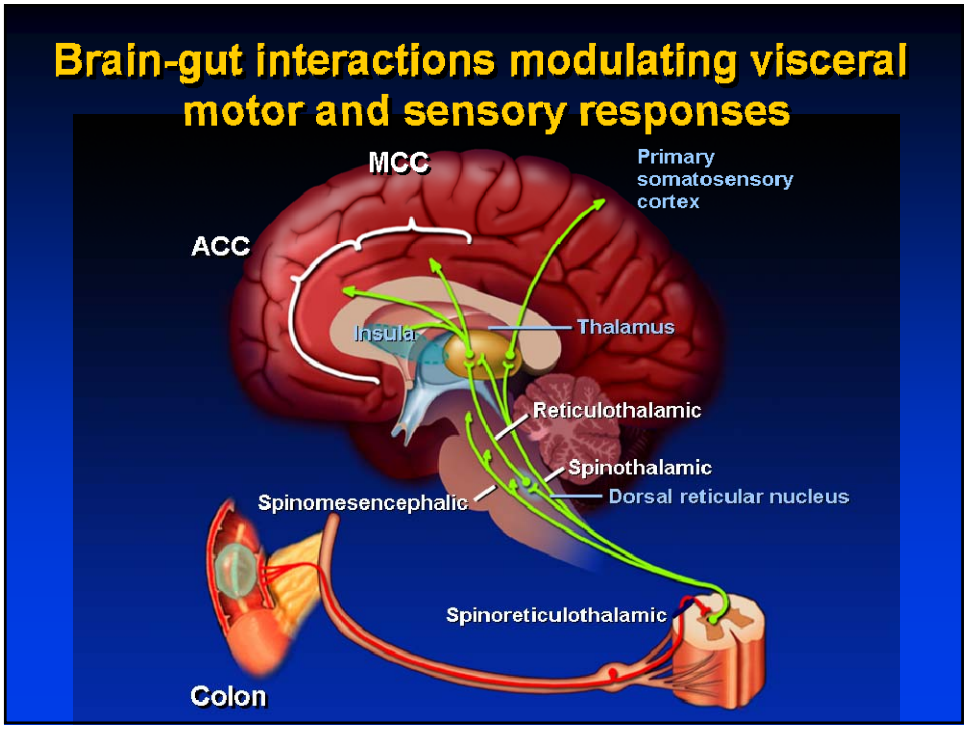


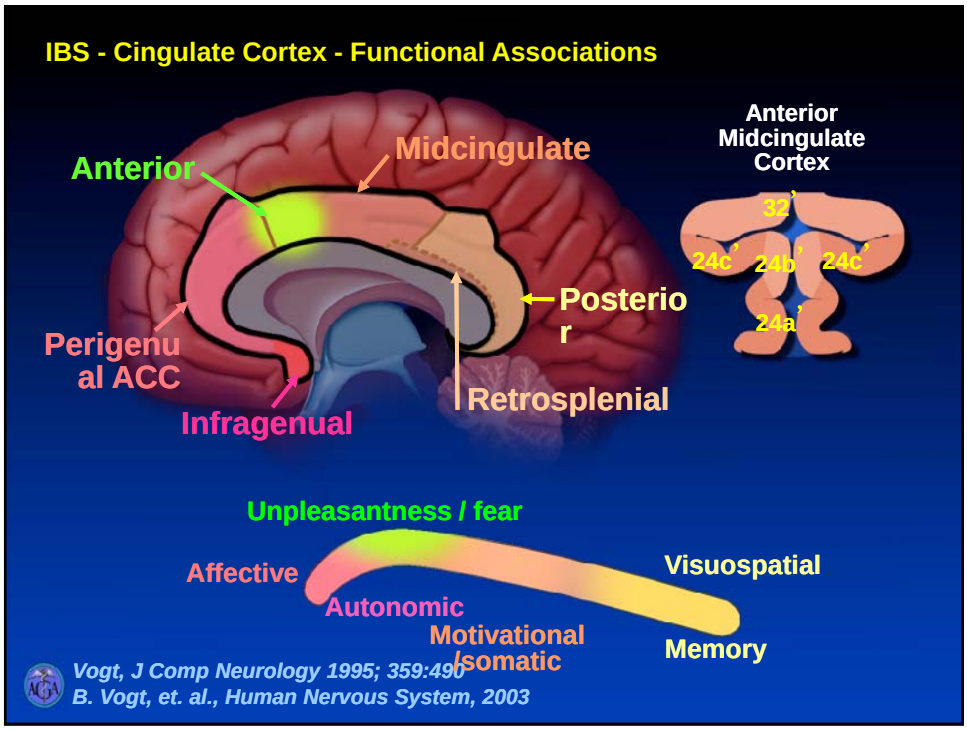
IPAN = intrinsic primary afferent neuron; 5-HT = serotonin.
Adapted from Grider JR et al. *Gastroenterology.* 1998;115:370-380.
Adapted from Gershon MD. *Rev Gastroenterol Disord.* 2003;3:S25-S34.

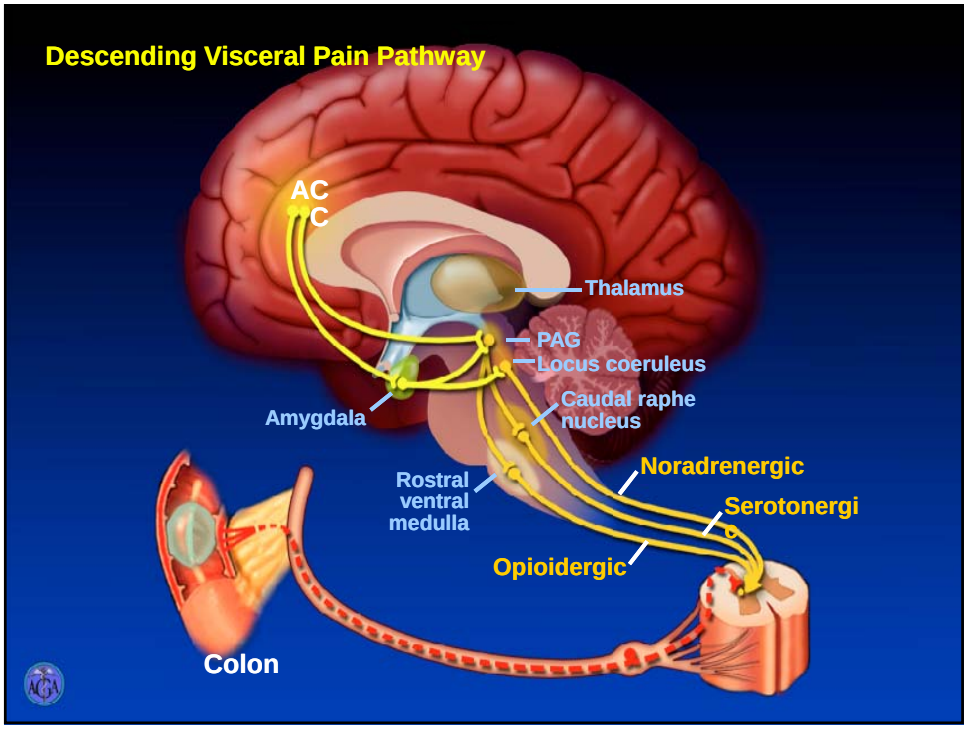
Normal Signals, Transmitted by Normal Sensory Nerves lead to Normal Sensations

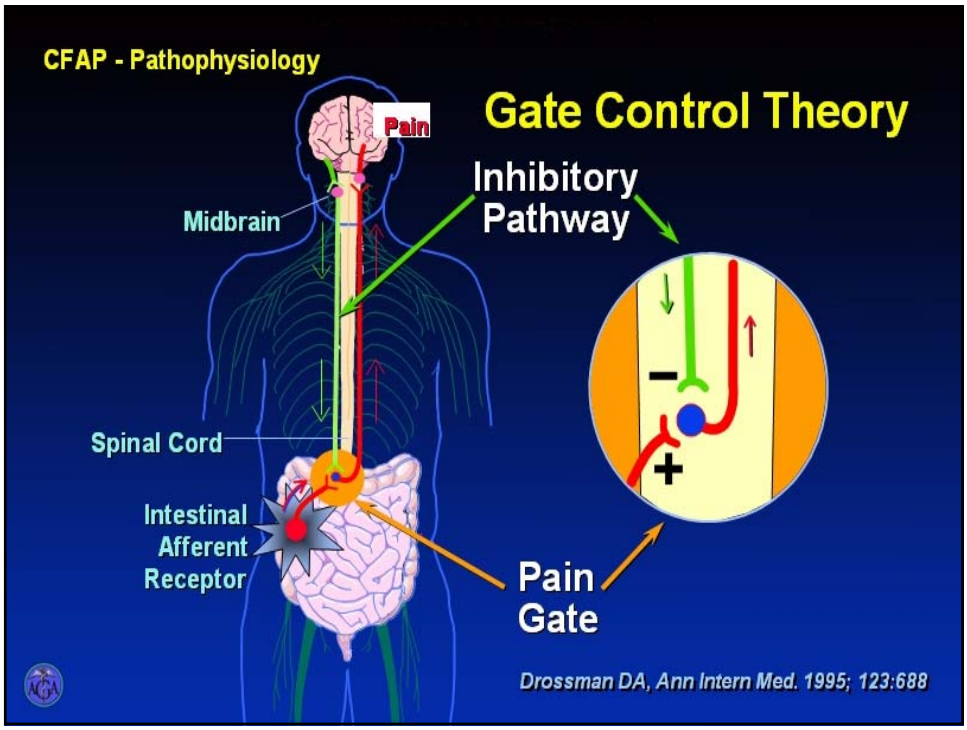


Gebhart GF 2000. *Am J Physiol* 278: G834-838
Grundy D (2004) *Gut* 53(Suppl II):ii5–ii8


Brain-gut interactions modulating visceral motor and sensory responses
MCC
Primary somatosensory cortex
ACC
Insula
Thalamus
Reticulothalamic
Spinothalamic
Dorsal reticular nucleus
Spinomesencephalic
Spinoreticulothalamic
Colon


IBS - Cingulate Cortex - Functional Associations
Anterior
Midcingulate
Posterior
Perigenual ACC
Infragenual
Retrosplenial
Anterior Midcingulate Cortex
32'
24c'
24b'
24c'
24a'
Unpleasantness / fear
Affective
Autonomic
Motivational
Isomatic
Visuospatial
Memory
Vogt, J Comp Neurology 1995; 359:490
B. Vogt, et. al., Human Nervous System, 2003


Descending Visceral Pain Pathway
AC
C
Thalamus
PAG
Locus coeruleus
Caudal raphe nucleus
Amygdala
Rostral ventral medulla
Noradrenergic
Serotonergi
Opioidergic
Colon


CFAP - Pathophysiology
Gate Control Theory
Pain
Midbrain
Inhibitory Pathway
Spinal Cord
Intestinal Afferent Receptor
Pain Gate
Drossman DA, Ann Intern Med. 1995; 123:688

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

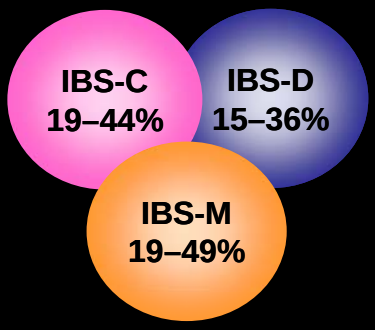
Longstreth et al, Gastroenterology 2006; 130:1480

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