

Irritable Bowel Syndrome and Chronic Constipation

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Treatment of IBS

Abdominal pain / discomfort

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

Bloating

- Tegaserod
- Dietary changes
- ? Probiotics
- ? Antibiotics

Constipation

- Fiber
- MOM/PEG solution
- Tegaserod

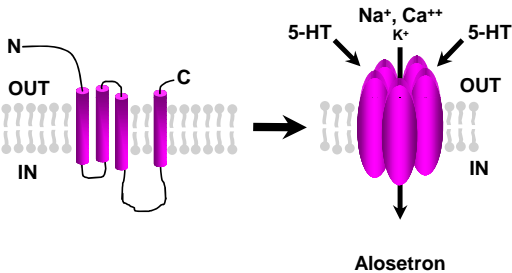
Diarrhea

- Loperamide
- Other opioids
- Alosetron

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

Alosetron (Lotronex) 2000

5-HT₃ Antagonist: Mechanisms of Action



Alosetron

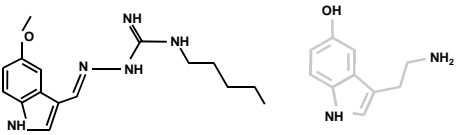
Kim D-Y, Camilleri M. Am J Gastroenterol. 2000;95:2698-2709.

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, Alimant Pharmacol Ther 2001; 15: 277

Effect of tegaserod on additional dysmotility symptoms of IBS-C¹

↑ Improved stool consistency

↑ Increased number of BMs/wk

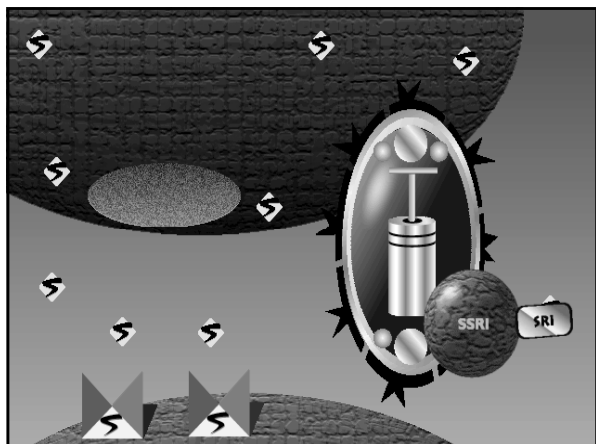
↓ Reduced straining

↓ 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

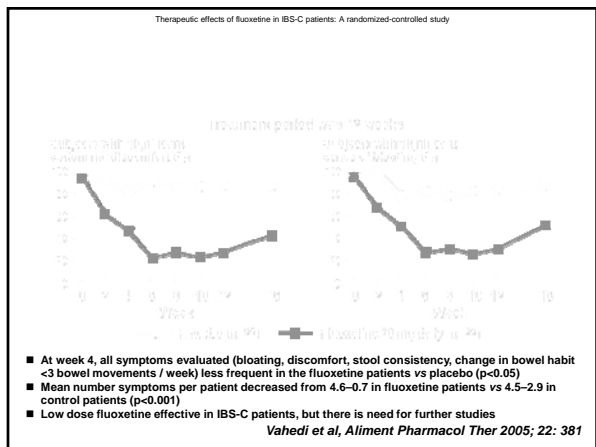
¹Kellow et al, Gut 2003; 52: 671
²Patrick et al, Gastroenterol 2005; 128: A287



Serotonin Transporter (SERT)

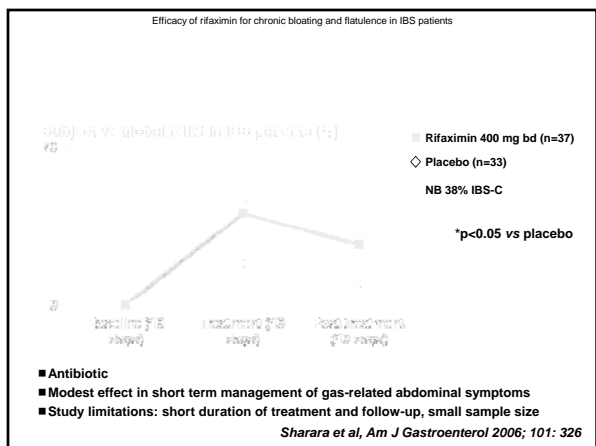
- Single protein
- Mediates reuptake of 5-HT from the synaptic cleft
- SERT in the **gut** is similar to SERT in the **brain** of the same species
- neurons (ENS) and crypt epithelial cells synthesize SERT proteins
- Function of the SERT: to control the concentration + actions of 5-HT in the gut and 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



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



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

Symptom	CC	IBS-C
Bloating	+++	+++
Abdominal discomfort	+++	+++
IBS-C	+++	+++
Rectal pain/discomfort	++	+++
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

A




Normal
≤5 markers remain

B



Slow-transit
Rings are scattered throughout the colon

C




Functional outlet obstruction
Rings are gathered in the rectosigmoid

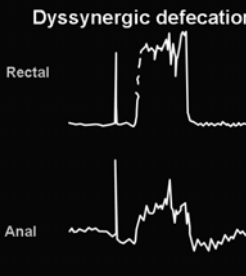
Falgel et al, *Clin Cornerstone* 2002; 4: 11

Manometry in patients with dyssynergia

Normal



Dyssynergic defecation



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

Efficacy of PEG-3350 in constipation

Number of BMs / wk

*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

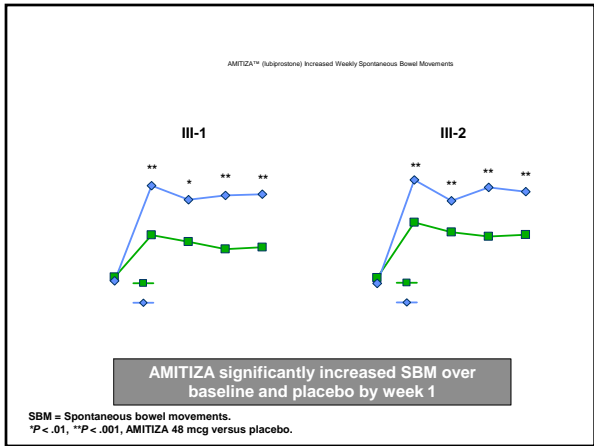
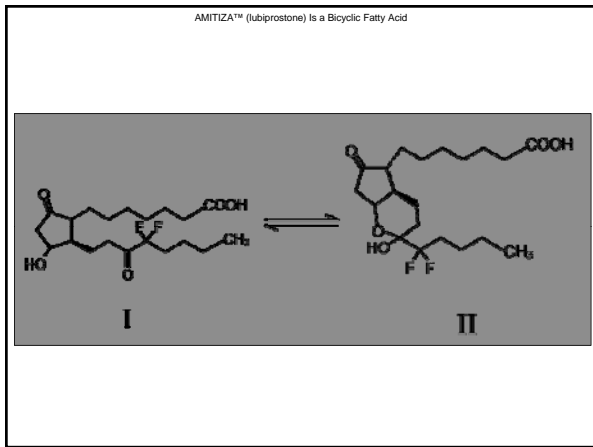
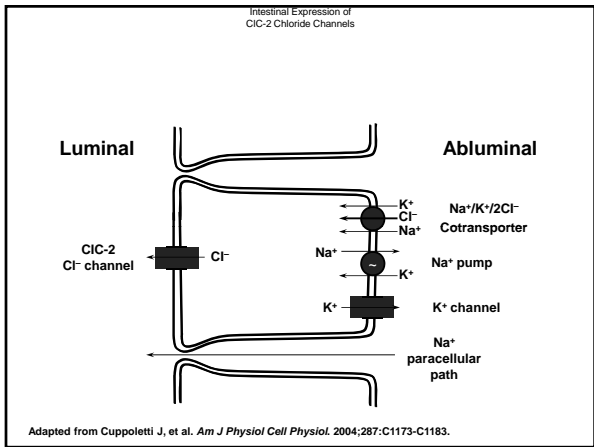
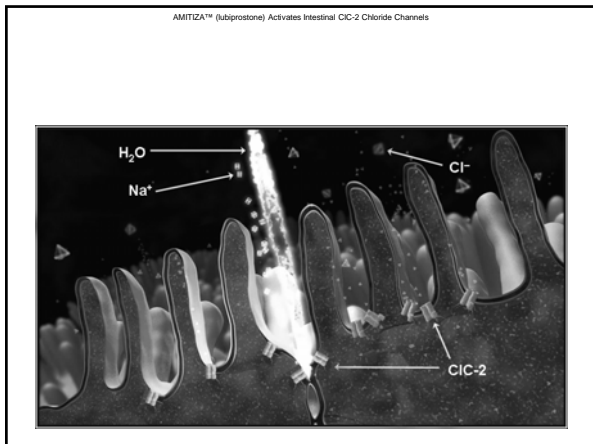
DiPalma et al, *Am J Gastroenterol* 2000; 95: 446
 Physician's Desk Reference 2005; 1025
 Coremans et al, *Dig Liver Dis* 2005; 37: 97

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

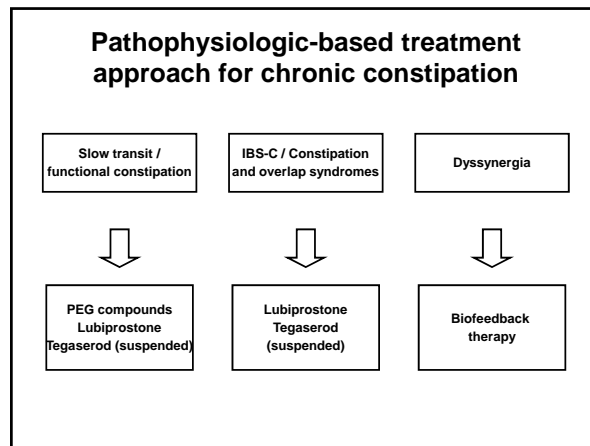


- AMITIZA™ (lubiprostone) Activates ClC-2 Chloride Channels
- Specific chloride channel-2 (ClC-2) activator
 - Promotes fluid secretion
 - Enhances intestinal fluid secretion to facilitate increased motility
- Ueno R, et al. *Gastroenterology*. 2004;126(suppl 2):A298. Abstract M1109.

Comparison of lubiprostone and tegaserod in CC

	Lubiprostone ¹	Tegaserod ² (Suspended)
Indication		
Mechanism of action		
Indications		
Administration		
Time to first response (TFR) in first 24 hours ^{3,4}		
Adverse events in CC ⁵		

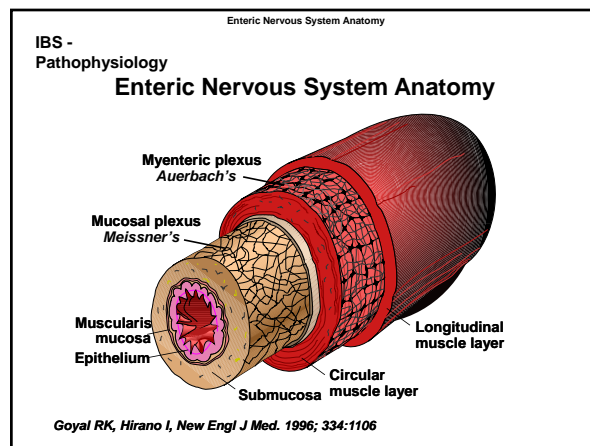
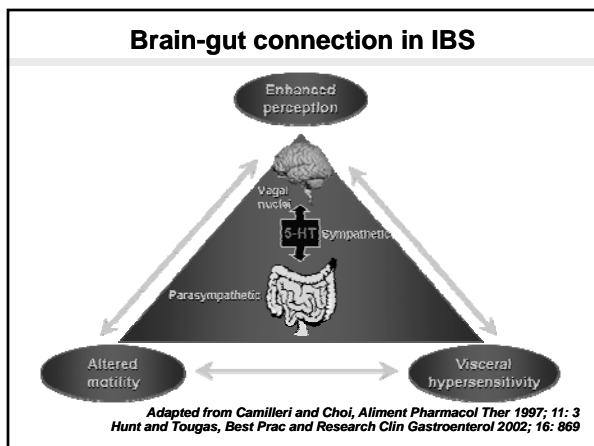
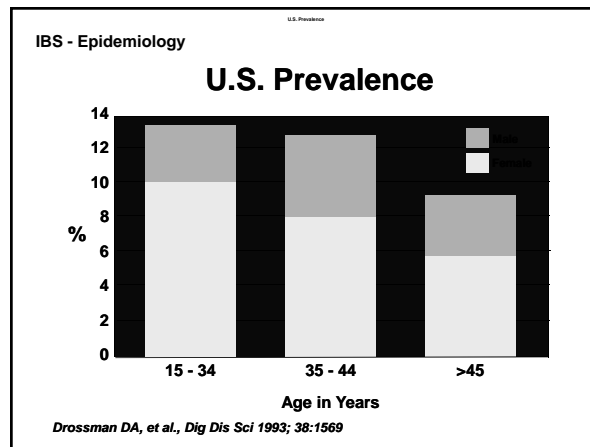
¹Lubiprostone PI
²Tegaserod PI
³AE rates for tegaserod in IBS-C are not listed here
⁴Rate reported in IBS-C, only aggravated headache listed for CC (1%)
⁵Johanson, Am J Gastroenterol 2005; 100: S324
⁶Kamm, Am J Gastroenterol 2005; 100: 362

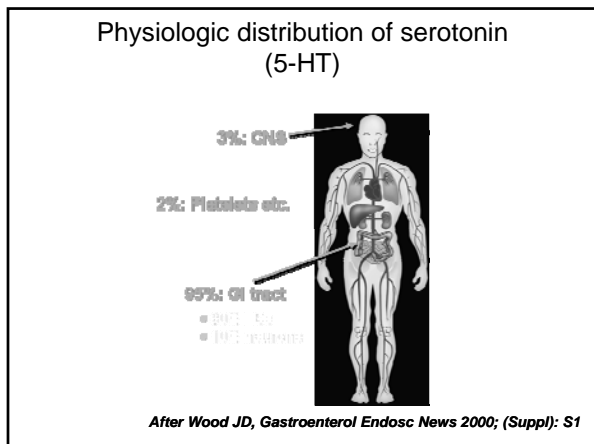


What is IBS?

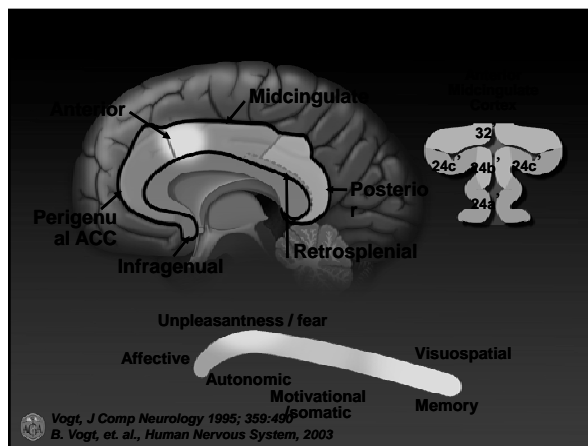
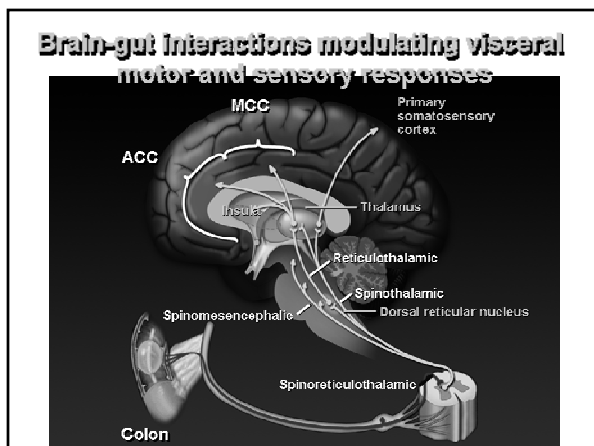
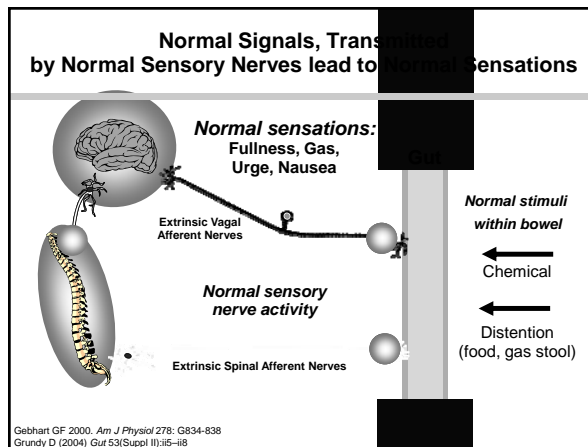
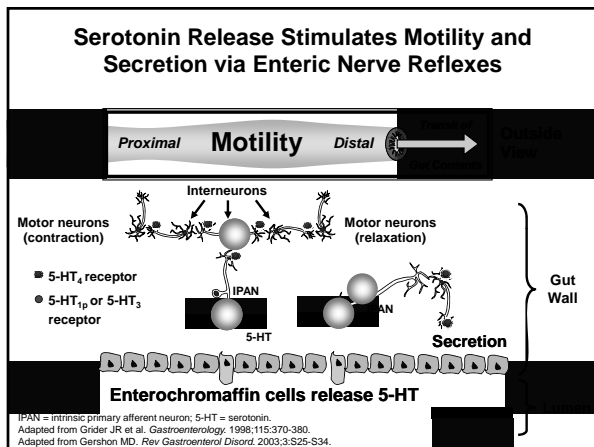
- a chronic, intermittent gastrointestinal condition
- a FUNCTIONAL bowel disorder without evidence of structural or biochemical abnormalities
- characterized by **ABDOMINAL PAIN or DISCOMFORT** associated with altered bowel function:
 - diarrhea
 - constipation
 - bloating or feeling of distension
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

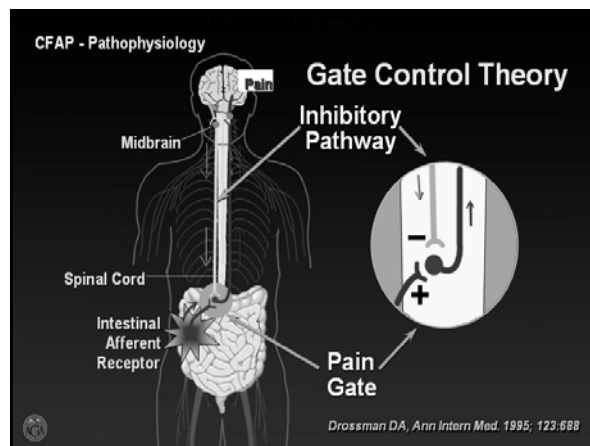
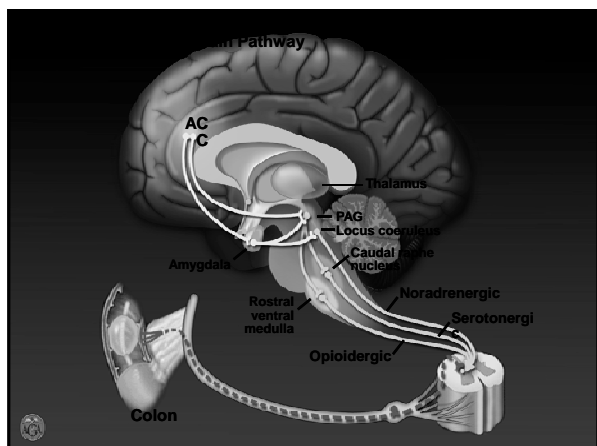
Drossman et al, Gastroenterology 1997; 112: 2120





- ### Some possible mediators of 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





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

IBS-C
19–44%

IBS-D
15–36%

IBS-M
19–49%

■ 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