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**

![Graph showing U.S. prevalence of IBS by age group and gender.](image)


**IBS - Physiologic Research**

- Stress affects GI function
- Pain sensitivity
- Clustered contractions
- CNS / ENS Autonomic reactivity
  - Meals
  - Pain / motility
  - 3 cpm motility
  - Visceral hypersensitivity
  - Post-infectious IBS

**Time Line of Physiologic Research in 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

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

Muscularis mucosa
Epithelium
Submucosa
Circular muscle layer
Longitudinal muscle layer
Mucosal plexus
Meissner’s
Myenteric plexus
Auerbach’s
Physiologic distribution of serotonin (5-HT)

3%: CNS
2%: Platelets etc.
95%: GI tract
- 90% ECs
- 10% neurons

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 Gershon MD. Rev Gastroenterol Disord. 2003;3:S25-S34.

Enterochromaffin cells release 5-HT

Brain-gut interactions modulating visceral motor and sensory responses

MCC = medial prefrontal cortex; ACC = anterior cingulate cortex; MCC = midcingulate cortex; Thalamus; Reticulothalamic tract; Spinothalamic tract; Dorsal reticular nucleus; Spinomesencephalic tract; Spinoreticulothalamic tract; Colon.
IBS - Cingulate Cortex - Functional Associations

Unpleasantness / fear

Affective

Autonomic

Motivational

Visuospatial

Somatic

Memory

Descending Visceral Pain Pathway

AC

Thalamus

PAG

Locus coeruleus

Caudal raphe nucleus

Noradrenergic

Serotonergic

Opioidergic

Colon

Anterior Midcingulate Cortex

Perigenual ACC

Infragenual

Retrospenial


Downing Visceral Pain Pathway
Brain - Gut Inhibitory Pain Pathway ("Gate Control")

Extrinsic Spinal Afferent Nerves

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

Normal sensations:
Fullness, Gas, Urge, Nausea

Normal sensory nerve activity

Extrinsic Spinal Afferent Nerves
Extrinsic Vagal Afferent Nerves

Normal stimuli within bowel
Chemical
Distention (food, gas stool)

**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
Mearin et al, Eur J Gastroenterol Hepatol 2003; 15: 165
Tillisch et al, Am J Gastroenterol 2005; 100: 896
Drossman et al, Gastroenterology 2005; 128: 580
Treatment of IBS

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

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

Altered bowel function
- Constipation
  - Fiber
  - MOM/PEG solution
  - Tegaserod

Diarrhea
- Loperamide
- Other opioids
- Alosetron

Alosetron (Lotronex) 2000
5-HT₃ Antagonist: Mechanisms of Action

Mechanisms of Action of 5-HT3 receptor antagonists

- Delay small bowel and colonic transit\textsuperscript{1,2}
  - treat diarrhea
- Increase colonic compliance\textsuperscript{1}
  - improve fecal urgency
- Inhibit chloride secretion\textsuperscript{1}
  - make stools more formed
- Blunt the gastrocolonic response\textsuperscript{1}
  - improve urgency
- Affect visceral afferent\textsuperscript{1}
  - diminish abdominal pain

Tegaserod (Zelnorm) 2002

- Tegaserod is a 5-HT\textsubscript{4} 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

Reduced sensations = reduced symptoms

1. REDUCED stimuli within bowel

2. REDUCED sensory nerve activity

Reduced sensations = reduced symptoms


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

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**

- 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

Efficacy of rifaximin for chronic bloating and flatulence in IBS patients

Rifaximin 400 mg bd (n=37)
Placebo (n=33)
NB 38% IBS-C

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

* p<0.05 vs placebo

CHRONIC CONSTIPATION

IDIOPATHIC
Prevalence and incidence of constipation in the US

- **Prevalence:**
  - estimated
  - 55 million Americans
    (prevalence 28%)
  - men: 12\%
  - women: 16\%
  - elderly individuals: 40\%

- **Onset rate 40 / 1000 person-years**

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1. Locke et al, Gastroenterology 2000; 119: 1766
2. Stewart et al, Am J Gastroenterol 1999; 94(12): 3530
Chronic Constipation and IBS-C Share GI Dysmotility Symptoms

<table>
<thead>
<tr>
<th>Symptoms &gt;3 months</th>
<th>Chronic Constipation</th>
<th>IBS-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Straining</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Hard/lumpy stools</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>&lt;3 BM/wk</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Feeling of incomplete evacuation</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Bloating/abdominal distension</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Abdominal pain/discomfort</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

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

IBS-C = irritable bowel syndrome with constipation.

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Functional subtypes of idiopathic constipation

- Slow transit constipation 47%
- Dyssynergic defecation 59%
- Irritable bowel syndrome 58%

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

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

Normal

Dyssynergic defecation

Rectal

Rectal

Anal

Anal

Pathophysiologic-based treatment approach for chronic constipation

- Slow transit / functional constipation
- IBS-C / Constipation and overlap syndromes
- Dyssynergia

PEG compounds
- Tegaserod
- Lubiprostone

Tegaserod

Biofeedback therapy

Biofeedback Therapy for Dyssynergic Constipation
(Randomized Controlled Trial)

Mean cSMBM per week ± S.E.M.

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>End Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biofeedback</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Sham</td>
<td></td>
<td>†</td>
</tr>
<tr>
<td>Standard</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P = 0.0018 vs. baseline
†P = 0.048 vs. standard

% of patients with dyssynergia after treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Biofeedback</th>
<th>Sham</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>21</td>
<td>21</td>
<td>23</td>
</tr>
</tbody>
</table>

*P = 0.0001 vs. sham, standard, and baseline

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

*p<0.01  
**p<0.001

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

AMITIZA™ (lubiprostone) Is a Bicyclic Fatty Acid

AMITIZA™ (lubiprostone) Increased Weekly Spontaneous Bowel Movements

SBM = Spontaneous bowel movements.

*P < .01, **P < .001, AMITIZA 48 mcg versus placebo.
AMITIZA™ (lubiprostone) Activates CIC-2 Chloride Channels

- Specific chloride channel-2 (CIC-2) activator
- Promotes fluid secretion
- Enhances intestinal fluid secretion to facilitate increased motility


Comparison of lubiprostone and tegaserod in CC

<table>
<thead>
<tr>
<th>Description</th>
<th>Lubiprostone¹</th>
<th>Tegaserod²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Chloride channel activator</td>
<td>5-HT₄ agonist</td>
</tr>
<tr>
<td>Indications</td>
<td>CC in male and female patients</td>
<td>CC in male and female patients ≤65 years, IBS-C in female</td>
</tr>
<tr>
<td>Administration</td>
<td>Twice daily orally with food</td>
<td>Twice daily orally before meals</td>
</tr>
<tr>
<td>Patients experiencing SBM in first 24 hours³,⁴†</td>
<td>Lubiprostone 61.3%</td>
<td>Tegaserod 62%</td>
</tr>
<tr>
<td>Adverse Events in CC*</td>
<td>Diarrhea (13%)</td>
<td>Diarrhea (7%)</td>
</tr>
<tr>
<td></td>
<td>Headache (13.2%)</td>
<td>Headache (15%)</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain (6.7%)</td>
<td>Abdominal pain (5%)</td>
</tr>
<tr>
<td></td>
<td>Nausea (61.1%)</td>
<td>Nausea (5%)</td>
</tr>
</tbody>
</table>

¹Different endpoints make the trials difficult to compare
²AE rates for tegaserod in IBS-C are not listed here
³Rate reported in IBS-C, only aggravated headache listed for CC (1%)
⁴Johanson, Am J Gastroenterol 2005; 100: S324
⁵Kamm, Am J Gastroenterol 2005; 100: 362
FDA-approved prescription medications for constipation

All constipation

Occasional

- Lexatives
  - PEG
  - Lactulose

Chronic

- Chronic idiopathic constipation
  - Tegaserod
  - Lubiprostone

- IBS with constipation
  - Tegaserod