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

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

Diarrhea
- Loperamide
- Other opioids
- Alosetron

Brandt, Am J Gastroenterol 2002; 97; S7
Drossman, Gastroenterology 2002; 123; 2108
Mechanisms of Action of 5-HT3 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

Tegaserod (Zelnorm)
2002

- 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

- Improved stool consistency
- Increased number of BMs/wk
- Reduced straining
- Relieved bloating
- Reduced abdominal pain / discomfort

1. 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$^2$
2. Efficacy beyond 12 weeks has not been studied
3. 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

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 4.6–6.7 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)**
- **Placebo (n=33)**

Note: 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*

**CHRONIC IDIOPATHIC CONSTIPATION**
Chronic Constipation and IBS-C Share GI Dysmotility Symptoms

IBS-C = irritable bowel syndrome with constipation.


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.

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
**Efficacy of PEG-3350 in constipation**

<table>
<thead>
<tr>
<th></th>
<th>Number of BMs / wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>PEG-3350: &lt;2, 2</td>
</tr>
<tr>
<td></td>
<td>Placebo:</td>
</tr>
<tr>
<td>Week 1</td>
<td>PEG-3350: 4.2, 2.9</td>
</tr>
<tr>
<td></td>
<td>Placebo:</td>
</tr>
<tr>
<td>Week 2</td>
<td>PEG-3350: 4.5, 2.7</td>
</tr>
<tr>
<td></td>
<td>Placebo:</td>
</tr>
</tbody>
</table>

- 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 CIC-2 Chloride Channels
Intestinal Expression of ClC-2 Chloride Channels


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.

- Specific chloride channel-2 (ClC-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 (Suspended)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Chloride channel activator</td>
<td>5-HT₄ agonist</td>
</tr>
<tr>
<td>Increases intestinal fluid secretion</td>
<td>Stimulates the peristaltic reflex</td>
<td></td>
</tr>
<tr>
<td>Inhibits visceral sensitivity</td>
<td>Stimulates intestinal secretion</td>
<td></td>
</tr>
<tr>
<td>Indications</td>
<td>CC in male and female patients</td>
<td>CC in male and female patients &lt;65 years, IBS-C in female patients</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 hours³⁴</td>
<td>Lubiprostone 61.3%</td>
<td>Tegaserod 62%</td>
</tr>
<tr>
<td>Adverse Events in CC*</td>
<td>Diarrhea (13%) Headache (13.2%) Abdominal pain (6.7%) Nausea (31.1%)</td>
<td>Diarrhea (7%) Headache (15%) Abdominal pain (5%) Nausea (5%)</td>
</tr>
</tbody>
</table>

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**Different endpoints make the trials difficult to compare**

*All rates for tegaserod in IBS-C are not listed here
**Rate reported in IBS-C, only aggravated headache listed for CC (1%)

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### Pathophysiologic-based treatment approach for chronic constipation

- **Slow transit / functional constipation**
  - PEG compounds
  - Lubiprostone
  - Biofeedback therapy

- **IBS-C / Constipation and overlap syndromes**
  - Lubiprostone
  - Tegaserod (suspended)

- **Dyssynergia**

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¹Lubiprostone PI
²Tegaserod PI
³Johanson, Am J Gastroenterol 2005; 100: S324
⁴Kamm, 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_

IBS - Epidemiology

U.S. Prevalence

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

Enteric Nervous System Anatomy

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

Enterochromaffin cells release 5-HT

Motor neurons (contraction)

Interneurons

Motor neurons (relaxation)

5-HT4 receptor

5-HT3 or 5-HT3 receptor

IPAN

5-HT

Secretion

Gut Wall

Lumen

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

Normal sensations:
Fullness, Gas, Urge, Nausea

Brain-gut interactions modulating visceral motor and sensory responses

IBS - Cingulate Cortex - Functional Associations

Vogt, J Comp Neurology 1995; 359:49
B. Vogt, et. al., Human Nervous System, 2003
Descending Visceral Pain Pathway

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

Gate Control Theory
Inhibitory 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

<table>
<thead>
<tr>
<th>IBS-C:</th>
<th>&gt;25% hard or lumpy stools and &lt;25% loose or watery stools</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS-D</td>
<td>&gt;25% loose or watery stools and &lt;25% hard or lumpy stools</td>
</tr>
<tr>
<td>IBS-M</td>
<td>&gt;25% loose or watery stools and &gt;25% hard or lumpy stools</td>
</tr>
<tr>
<td>IBS-U</td>
<td>Insufficient abnormality of stool consistency to meet criteria for IBS-C, IBS-D, or IBS-M</td>
</tr>
</tbody>
</table>

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: 185
Tillisch et al, Am J Gastroenterol 2005; 100: 896
Drossman et al, Gastroenterology 2005; 128: 580