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: >3BM/ day, loose stools, urgency
  - constipation: <3BM/wk, hard/lumpy stools, straining
  - bloating or feeling of distension
  - sense of incomplete evacuation
  - passage of mucus

*Drossman et al, Gastroenterology 1997; 112: 2120*
Brain-gut connection in IBS

Adapted from Camilleri and Choi, Aliment Pharmacol Ther 1997; 11: 3
Hunt and Tougas, Best Pract 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
Physiologic distribution of serotonin (5-HT)

3%: CNS

2%: Platelets etc.

95%: GI tract
- 90% ECs
- 10% neurone

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 (5-HT) and motor activity

Some IBS Symptoms May Be Mediated by 5-HT Receptors in the Colon

Adapted from Grider et al, Gastroenterology 1998; 115: 370
Gershon, Rev Gastroenterol Dis 2003; 3: S25
IBS - Cingulate Cortex - Functional Associations

Unpleasantness / fear
Affective
Motivational/somatic
Visuospatial
Memory

Descending Visceral Pain Pathway

Noradrenergic
Serotonergic
Opioidergic

Colon

AC
Thalamus
PAG
Locus coeruleus
Caudal raphe
nucleus
Rostral ventral medulla
Amygdala

B. Vogt, et. al., Human Nervous System, 2003
Brain - Gut Inhibitory Pain Pathway ("Gate" Control)

Treatment of IBS

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

Bloating / distention

Altered bowel function

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

Some IBS Symptoms May Be Mediated by 5-HT Receptors in the Colon

Adapted with permission from Professor David Grundy, Department of Biomedical Science, The University of Sheffield.
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$_4$ receptor agonist
- new class of compound: aminoguanidine indoles
- Structure similar to serotonin

Camilleri, Aliment Pharmacol Ther 2001; 15: 277

Serotonin (5-HT)

\[
\begin{align*}
\text{NH} & \quad \text{O} \\
\text{O} & \quad \text{NH} \\
\text{N} & \quad \text{NH}
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \quad \text{NH} \\
\text{NH} & \quad \text{NH}_2
\end{align*}
\]

Tegaserod

Adapted from Grider et al, Gastroenterology 1998; 115: 370
Gershon, Rev Gastroenterol Dis 2003; 3: S25

Tegaserod is a 5-HT$_4$ agonist

Orad motor neurons (contraction) Ach / BP

Caudal motor neurons (relaxation) VIP / NO

Interneurons in the myenteric plexus

CGRP

IPAN

Enterochromaffin cells release 5-HT

Movement of gut content

Adapted from Grider et al, Gastroenterology 1998; 115: 370
Gershon, Rev Gastroenterol Dis 2003; 3: S25
Effect of 5HT₄ Agonist on Colonic Transit

Pre-treatment

C-IBS

Post-Tegaserod

6 hr 24 hr 48 hr

Effect of Tegaserod on Colonic Transit

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

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

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

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
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

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

Overlap in IBS-C and chronic constipation (CC)

At least 12 weeks, which need not be consecutive, in the preceding 12 months:

**IBS-C**
- Abdominal pain / discomfort associated with two or more of the following:
  - <3 BMs per week
  - hard or lumpy stools
  - relieved with BM
- May also be associated with:
  - bloating, feeling of abdominal distension, passage of mucus, straining
  - incomplete evacuation
  - may alternate with diarrhea

**CC**
- Two or more of the following:
  - <3 BMs per week
  - >25% of BMs:
    - hard or lumpy stool
    - straining
    - incomplete evacuation
    - sensation of anorectal obstruction / blockage
    - manual maneuvers to facilitate

BM = bowel movement

Thompson et al, Gut 1999; 45: ll43
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


Summary:
Pathophysiology of chronic constipation

- Slow-transit constipation:
  - impaired colonic and rectosigmoid contractile response
  - reduced colonic propulsion of stool with slower transit
  - fewer serotonin cells in the colon
  - abnormalities in serotonin receptor protein
  - absent or decreased number of interstitial cells of Cajal

- Dyssynergic defecation:
  - impaired co-ordination of muscles involved in defecation
  - impaired sensation

- IBS with constipation:
  - primary complaint is abdominal pain
  - altered release and re-uptake of serotonin
Pathophysiologic-based treatment approach for chronic constipation

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

- PEG compounds
- Tegaserod
- Lubiprostone

Biofeedback therapy

Biofeedback Therapy for Dyssynergic Constipation
(Randomized Controlled Trial)

Mean CSBMs per week ± S.E.M.

- Baseline
- End Active

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

% of patients with dyssynergia after treatment

*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
Chronic constipation = <3 SBM per week. Minimum of 6-month history
SBM = Any BM that did not occur within 24 hours of rescue laxative use

![Bar chart showing SBM 24 hours post-first dose (%) for Placebo (n=118) and Lubiprostone 24 ug bid (n=119).]

**Phase III, double-blind, placebo-controlled trial of lubiprostone vs placebo 28 days**

- **SBM 24 hours post-first dose (%)**
  - Placebo (n=118)
  - Lubiprostone 24 ug bid (n=119)

**Comparison of lubiprostone and tegaserod in CC**

<table>
<thead>
<tr>
<th></th>
<th>Lubiprostone(^1)</th>
<th>Tegaserod(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
<td>Chloride channel activator</td>
<td>5-HT(_4) agonist</td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Increases intestinal fluid secretion</td>
<td>Stimulates the peristaltic reflex; Stimulates intestinal secretion; Inhibits visceral sensitivity</td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td>CC in male and female patients</td>
<td>CC in male and female patients &lt;65 years, IBS-C in female</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Twice daily orally with food</td>
<td>Twice daily orally before meals</td>
</tr>
<tr>
<td><strong>Patients experiencing SBM in first 24 hours(^3,4)</strong></td>
<td>Lubiprostone 61.3%</td>
<td>Tegaserod 62%</td>
</tr>
<tr>
<td><strong>Adverse Events in CC(^*)</strong></td>
<td>Diarrhea (13%) Headache (13.2%) Abdominal pain (6.7%) Nausea (51.1%)</td>
<td>Diarrhea (7%) Headache (15%(^*)) Abdominal pain (5%) Nausea (6%)</td>
</tr>
</tbody>
</table>

\(^1\)Different endpoints make the trials difficult to compare
\(^2\)AE rates for tegaserod in IBS-C are not listed here
\(^3\)Rate reported in IBS-C, only aggravated headache listed for CC (1%)

\(^*\)Johanson et al, Am J Gastroenterol 2005; 100: S324
\(^*\)Kamm, Am J Gastroenterol 2005; 100: S328
FDA-approved prescription medications for constipation

- All constipation
  - Occasional
  - Chronic
    - Laxatives: PEG, lactulose
    - Chronic idiopathic constipation: Tegaserod, Lubiprostone
    - IBS with constipation: Tegaserod

THE END