Irritable Bowel Syndrome: Past, Present, and Future

G. Nicholas Verne, M.D.
Professor and Division Director
Division of Gastroenterology, Hepatology, Nutrition
Department of Internal Medicine
Ohio State University
Columbus, OH

Prevalence of IBS in the US

Drossman et al., Dig Dis Sci, 1993

Prevalence of IBS Diagnosis

Mitchell & Drossman, Gastroenterology, 1987

Quality-of-life impact of IBS vs other conditions

Frank et al, Clin Ther 2002
Medical Costs Associated With IBS

- IBS results in an estimated $8 billion in direct medical costs annually
- IBS sufferers incur 74% more direct healthcare costs than non-IBS sufferers
- IBS patients have more physician visits for both GI and non-GI complaints

Talley et al., Gastroenterology, 1995

Stool Character-Description

IBS: Symptoms

Chronically recurring symptoms
- Abdominal pain
- Altered bowel function
- Incomplete evacuation
- Urgency
- Bloating

Stool Character-Description

Prevalence by IBS subgroups

Survey respondents (%)

Talley et al, 1995
1. At least 12 weeks, which need not be consecutive, in the past 12 months of abdominal discomfort or pain that has 2 of 3 features:
- Relieved by defecation and/or
- Associated with a change in frequency of stool, and/or
- Associated with a change in consistency of stool

2. 2 or more of the following at least 25% of the time:
- Altered stool frequency
- Altered stool form
- Altered stool passage (straining, urgency, feeling of incomplete evacuation)
- Passage of mucous
- Bloating or feeling of abdominal distension

Rome I-II Criteria

Rome III Criteria

Visceral Hypersensitivity in IBS

Visceral Pain Thresholds

Longstreth, Gastroenterology, 2006

Zhou et al., 2009

Whitehead et al., Dig Dis Sci, 1980
Somatic Hypersensitivity in IBS Patients

- IBS patients also exhibit a number of extra-intestinal symptoms such as migraine headaches, back and muscle pain
- Consistent with central hyperalgesic mechanism(s)
- Recent studies have suggested that somatic hyperalgesia may also occur in IBS patients

Zhou & Verne, 2008
Visceral Hypersensitivity: Pathophysiology

- Triggers: chemical, environmental, physical, stress, inflammatory
- Postulated mechanisms:
  - Hyperexcitability/activation of neurotransmitters (sub P, CGRP)
  - Modulation of nociceptive transmission (NMDA)
  - Recruitment of silent nociceptors
  - Loss of inhibitory modulation to dorsal horn neurons
  - Neuroplasticity leading to chronic visceral hypersensitivity

Mayer & Raybould, Gastroenterology, 1990
Mayer & Gebhart, Gastroenterology, 1994

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 and Camilleri, Am J Gastroenterol 2000
Grider et al., Gastroenterology 1998

Viscerosomatic Convergence

Verne et al., Gut, 2006
Plasma 5-HT levels in IBS

Controls (n=6) Controls (n=6) Meal Meal
1000 1000 1200 1200 1400 1400
5-HT (nmol/l) 5-HT (nmol/l) IBS patients (n=5) IBS patients (n=5)

IBS - Pathophysiology

Integration
Input
Effect

Bearcroft et al., Gut, 1998

Serotonin and EC cells in Altered GI Motility

Diarrhea
Increased circulating 5-HT

Constipation
Increased number of EC cells in post-infectious IBS
Decreased number of EC cells in constipation

Diagnostic Tests for IBS

If patient has typical features of IBS:

- Labs:
  - CBC, electrolytes, LFTs, TSH
- Stool studies:
  - Occult blood, leukocytes, O & P, Giardia lamblia antigen
- Endoscopy:
  - Sigmoidoscopy ± air-contrast barium enema or colonoscopy if ≥ 50 yrs

Bearcroft et al., Gut 1998
Spiller et al, Gut 2000
“Red Flags”

Additional diagnostic screening needed for atypical presentations such as:

- Anemia
- Fever
- Persistent diarrhea
- Rectal bleeding
- Severe constipation
- Weight loss
- Nocturnal symptoms of pain and abnormal bowel function
- Family history of GI cancer, inflammatory bowel disease, or celiac disease
- New onset of symptoms in patients 50+ years of age

Case Presentation

- 19 yowf with hx “refractory IBS”
- 12 year hx constipation, abdominal pain, and marked abdominal distension
- Previous workup including endoscopy: negative
- 3 weeks noted between spontaneous bowel movements
- On exam, marked distension of abdomen is noted with decreased bowel sounds
- KUB obtained:
Current Management of IBS

- Establish a positive diagnosis
- Reassure patient that there is no serious organic disease or alarming symptoms
- No “gold standard” treatment
- Existing therapies:
  - Marginal efficacy
  - Side effects
  - Target only 1 symptom

Available Treatments for IBS

<table>
<thead>
<tr>
<th>Anticholinergic/Antispasmodics</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCAs/SSRIs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloating</td>
</tr>
<tr>
<td>Altered Bowel Motility</td>
</tr>
</tbody>
</table>

| Loperamide                     |
| Cholestyramine                |
| Psyllium                      |
| Methylcellulose               |
| Calcium polycarbophil         |
| Lactulose                     |
| 70% sorbitol                  |
| PEG solution                  |
## Therapy of Functional Gut Pain: A Unique Problem

- Current treatment modalities are based on unproven pathophysiological concepts
- Placebo response rates vary from 20-88%
- Few therapies have ever been conclusively been shown to be superior to placebo in well designed studies

---

## Tricyclic Antidepressants and SSRIs

- Used for pain
- Reserved for patients with severe or refractory symptoms
  - Are effective for neuropathic pain
  - Have central analgesic/anticholinergic effects

---

## Placebo Response Rate in IBS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Studies</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall range 17-84%</td>
<td>10</td>
<td>472</td>
</tr>
<tr>
<td>Median 52%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean 55.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range 17-40%: 10 studies, n = 472</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range 41-60%: 8 studies, n = 557</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range 61-84%: 13 studies, n = 1440</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

## Low Dose TCAs: Possible Mechanisms of Analgesic Action

- Reuptake inhibition of NE and 5HT
- Receptor antagonism of H1, 5HT-2, D2, muscarinic sites
- NMDA receptor antagonist
- Induction of glucocorticoid receptor expression
- Direct effect on peripheral afferent nerves
Physiological Distribution of 5-HT

CNS – 5%

GI tract – 95%
- enterochromaffin cells
- neuronal

Serotonin (5-HT) Receptors in the Gut

- Currently 14 5-HT receptor or recognition sites identified:
  - 5-HT$_{1A}$, 5-HT$_{1P}$, 5-HT$_{1C}$, 5-HT$_2$, 5-HT$_3$, 5-HT$_4$ found in gut
  - 5-HT1: Inhibition of neurotransmitter release and increased smooth muscle contraction
  - 5-HT2: Contraction of gut smooth muscle

Serotonin (5-HT) Receptors in the Gut

<table>
<thead>
<tr>
<th>Pharmacologic Action</th>
<th>5-HT3 Antagonists</th>
<th>5-HT4 Agonists</th>
</tr>
</thead>
</table>

Gershon, Aliment Pharmacol Ther, 1999
Serotonin Agents

5-HT<sub>3</sub> Receptor Antagonists
- Alosetron
- Odansetron
- Cilansetron

5-HT<sub>4</sub> Receptor Agonists
- Cisapride
- Prucalopride
- Tegaserod

Alosetron in IBS

- Selective 5-HT<sub>3</sub> receptor antagonist
- Enhances jejunal water/salt absorption
- Increases colonic compliance
- Slows colonic transit
- FDA approved for women with diarrhea-predominant IBS

Alosetron Pain Relief in IBS

Alosetron: Contraindications

- Chronic or severe constipation
- History of intestinal obstruction, adhesions, perforation, or toxic megacolon
- Diverticulitis
- History of Crohn’s disease or ulcerative colitis
- Ischemic colitis
Serotonin (5-HT) and Motor Activity

Enterochromaffin cells release 5-HT

5-HT4 Receptors

• Selective 5HT4 receptor agonist
• Increases release of CGRP and Sub P
• Accelerates colonic transit
• Inhibition of afferent nerve activity
• Previously approved for women with constipation-predominant IBS
• Previously approved for men and women with chronic constipation

Lubiprostone

• Locally acting chloride channel activator
• Enhances chloride-rich intestinal fluid secretion
• Increases intestinal fluid secretion
• Increases motility in the gut
• Approved for Chronic Constipation (24 mcg bid)
• Approved for Constipation Predominant Irritable Bowel Syndrome (8 mcg bid)

Tegaserod

New Directions in IBS Treatment

• 5-HT3 receptor antagonists
• 5-HT4 receptor agonists
• Opioid-like agents (Mu, kappa receptor)
• Enkephalin/endorphin analogs
• NMDA receptor antagonists
• Substance P (NK-1) and CGRP antagonists
Sphincter of Oddi Dysfunction & Visceral Hyperalgesia

J. Royce Groce MD, MS
6/4/10

Sphincter of Oddi Dysfunction (SOD)

- Obstructive disorder occurring at the level of the Sphincter of Oddi
  - Benign
  - Noncalculous
- Pathogenesis relates to
  - Passive obstruction at the SO
    - Fibrosis
    - Inflammation
  - Active obstruction
    - Sphincter muscle spasm
Ductal Variants

Sphincter of Oddi Dysfunction

- Milwaukee Classification for Biliary SOD
  - Biliary Type I
    - Biliary-type pain
    - Serum AST or Alk Phos
      - >2 times normal
      - ≥2 occasions
    - Common bile duct >12 mm
    - Delayed ERCP contrast drainage
      - >45 minutes
      - Largely abandoned

- Biliary Type II
  - Biliary-type pain alone

- Biliary Type III
  - Biliary-type pain alone

- Pancreatic Type SOD
  - Pancreatic type pain
  - May lead to acute recurrent episodes of otherwise unexplained pancreatitis
  - Considered after biliary causes have been excluded
### “Biliary Type Pain”

- Comes on suddenly or builds rapidly to a peak over a few minutes
- It is a constant pain
  - Does not come and go
  - May vary in intensity while it is present
- It lasts for 15 minutes to 4-5 hours
  - Does not last for days, months or years

### “Biliary Type Pain”

- Most commonly felt locations
  - Middle of the upper abdomen just below the sternum
  - Right upper abdomen just below the margin of the ribs

### “Biliary Type Pain”

- The pain usually is severe
  - Movement does not make the pain worse
  - Pts often walk about or writhe in bed trying to find a comfortable position
- Often is accompanied by nausea

### “Biliary Type Pain”

- Atypical locations
  - Occasionally may be felt in the back at the lower tip of the scapula on the right side
  - Rare occasions, the pain may be felt beneath the sternum and be mistaken for angina or a heart attack
**Sphincter of Oddi Dysfunction**

- Postcholecystectomy pain resembling preoperative biliary pain
  - 10% to 20% of patients post-CCX
  - Most common explanation is that the symptoms before surgery were not caused by gallstones
  - Most likely diagnosis in this group of patients is a functional gastrointestinal disorder

**Sphincter of Oddi Manometry**

- Functional GI disorders
  - Irritable bowel syndrome
  - Nonulcer dyspepsia
  - Non-cardiac Chest Pain
  - SOD III?
    - 9 to 14% ofPts evaluated for Post-ccx pain
    - 30-60% in carefully selected patients
      - Typical Pain
      - Other causes excluded

[Image](http://www.cookmedical.com/esc/content/lg_thumbnail/esc_som.jpg)

[Image](http://www.gastrohep.com/images_pdfs/images/medium/1405120789_chapter_06_f4.jpg)
### Indications for Sphincter of Oddi Manometry

- Patients must have had a Cholecystectomy (CCX)
- Biliary stone disease must be excluded
- Patients must be willing to accept the high risks of ERCP with manometry
  - Post-ERCP pancreatitis
    - 15-20%
    - Reduced to < 5% with prophylactic PD stenting

### Indications for Sphincter of Oddi Manometry

- Suspected type III SOD
  - CCX
  - Biliary type pain
  - Rule out non-biliary causes
    - Therapeutic trial failure
      - PPI – GERD
      - Antispasmodic – IBS
      - Pain Modulator – Visceral Hyperalgesia

### Indications for Sphincter of Oddi Manometry

- Suspected type I SOD
  - CCX
  - Biliary type pain
  - “Academic curiosity”
- Suspected type II SOD
  - CCX
  - Biliary type pain

### Sphincter of Oddi Manometry

- **SOD Manometry**
  - Likelihood of elevated basal SO pressure
    - Type I - 86%
    - Type II - 55%
    - Type III – 28%

---

Endoscopic Biliary Sphincterotomy

Sphincter of Oddi Dysfunction

- Patients that fail to respond to Sphincterotomy may actually have a functional GI disorder and visceral hyperalgesia

Sphincter of Oddi Dysfunction

- Probability of Pain Relief from Sphincterotomy
  - Type I
    - Abnormal Mano = 90-95%
    - Normal Mano = 90-95%
  - Type II
    - Abnormal Mano = 85%
    - Normal Mano = 35%
  - Type III
    - Abnormal Mano = 55-60%
    - Normal Mano = <10%


Sphincter of Oddi Dysfunction

- One small study used an electronic barostat to assess GI tract sensitivity in patients with SOD type III
  - Exhibited duodenal hyperalgesia
  - Reproduced the characteristic symptoms
  - Did not have rectal hyperalgesia

**Biliary & Duodenal Hypersensitivity**

- Findings suggest a possible source of symptoms in patients with SOD III
- Provide a possible explanation for the high failure rate of pain relief after EBS and EPS


---

**Biliary & Duodenal Hypersensitivity**

- The neural connections and reflexes
  - Gallbladder (GB) to the SO
  - Gallbladder to stomach and duodenum
- GB and SO may influence gastroduodenal motility and thus sensitivity

## Biliary & Duodenal Hypersensitivity

- Sensory convergence in the dorsal horn of the spinal cord could lead to duodenal hyperalgesia in the presence of biliary duct hyperalgesia

One study evaluated 24 SOD patients with an elevated basal sphincter pressure, who did not respond to both EBS and EPS
- There was a high prevalence of abnormal duodenojejunal motility

---

## Visceral Hyperalgesia

- Chronic abdominal pain without a biological disease marker
- Similar to irritable bowel syndrome

### Pathophysiology
- Heightened perception has been postulated to develop from hyperexcitability of neurons in the dorsal horn
- May involve altered processing of nociceptive stimuli in the brain


Visceral Hyperalgesia

- The lack of objective findings in response to EBS and EPS in most patients with SOD type III suggests a potential role of visceral hyperalgesia
  - Arises from organs adjacent to the biliary tree


Conclusions

- There are 3 types of Biliary SOD
  - Biliary type Pain
  - Abnormal LFT's
    - Greater than 2x the upper limit of normal
    - Elevated on 2 separate occasions
    - Returns to normal in between attacks of pain
  - Dilated CBD
    - 12mm or greater

Treatment of Visceral Hyperalgesia

- Pt may be tried on low-dose tricyclic antidepressants
  - Nortriptyline (Pamelor)
- Patients who continue to have prominent pain
  - Duloxetine (Cymbalta)
  - Gabapentin (Neurontin)
  - Pregabalin (Lyrica)

Conclusions

- Not all RUQ abdominal pain is biliary pain
- The likelihood of response to spincterotomy depends on SOD type

Jay Pasricha, The Riddle, Mystery, and Enigma of Gastroparesis. THE JOURNAL OF SUPPORTIVE ONCOLOGYVOLUME 5, NUMBER 8 SEPTEMBER 2007
### Conclusions

**Prior to considering ERCP with manometry for type III SOD**
- Rule out CBD stones
- Give therapeutic trials of
  - PPI – GERD
  - Atispsamotic – IBS
  - Pain modulator – Visceral Hyperalgesia

### Conclusions

**There is some experimental evidence to support visceral hypersensitivity as a possible etiology for pain in SOD**
- Largely small non-randomized trials
- There is a paucity of recent work in this area

### Conclusions

**There appears to be some overlap in the symptoms of SOD III and the functional GI disorders**
- Controlled trials are needed to further elucidate the pathogenesis of these diseases so that we can more effectively target our therapy