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

Prevalence of IBS Diagnosis

Quality-of-life impact of IBS vs other conditions

Drossman et al., Dig Dis Sci, 1993

Mitchell & Drossman, Gastroenterology, 1987

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
  Alternator
  Diarrhea predominant
  Constipation predominant

- Incomplete evacuation
- Urgency
- Bloating

Prevalence by IBS subgroups

Survey respondents (%)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Females</th>
<th>Males</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS-constipation</td>
<td>5.2</td>
<td>3.5</td>
<td>6.7</td>
</tr>
<tr>
<td>IBS-diarrhea</td>
<td>5.5</td>
<td>5.3</td>
<td>5.6</td>
</tr>
<tr>
<td>IBS-alternating</td>
<td>5.2</td>
<td>5.6</td>
<td>5.4</td>
</tr>
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</table>

3022 residents surveyed in Minnesota
536 respondents

Talley et al., 1995
Rome I-II Criteria

1. At least 3 months of continuous or recurrent symptoms of abdominal pain or discomfort that is:
   ✓ 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:
   ✓ Alteration in stool frequency
   ✓ Alteration in stool form
   ✓ Alteration in stool passage (straining, urgency, feeling of incomplete evacuation)
   ✓ Passage of mucus
   ✓ Bloating or feeling of abdominal distension

Rome III Criteria

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
   ✓ Onset associated with a change in frequency of stool; and/or
   ✓ Onset associated with a change in form (appearance) of stool

IBS-Pathophysiology

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Stress affects GI function</th>
<th>Pain sensitivity</th>
<th>Clustered contractions</th>
<th>CNS / ENS Autonomic reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motility</td>
<td>Meals</td>
<td>Pain / motility</td>
<td>3 cpm motility</td>
<td>Visceral hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>1990</td>
<td>2000</td>
<td></td>
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</tbody>
</table>

Visceral Hypersensitivity in IBS

Visceral Pain Thresholds

Pain produced by rectosigmoid balloon distension

- Normal
- IBS

Viscera

Ascending pain pathway

Dorsal root ganglion

Brain stem

Spinal cord

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

Verne & Price, 2002
**Hot Water Immersion**

- Thermal Hyperalgesia in IBS

  - *P<0.001

  - Verne et al., Pain 2001

**Mechanical Visual Analogue Scale**

- Viscerosomatic Convergence

  - Verne et al., Gut 2006
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

Plasma 5-HT levels in IBS

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

Bearcroft et al., Gut 1998
Spiller et al., Gut 2000

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

IBS - Pathophysiology

Integration

- Cognition
- Affect
- Sight
- Sound
- Smell
- Somatosensory
- Viscerosensory
- Motility
- Secretion
- Blood Flow

“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

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Case Presentation

- 19 yo wf 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>Pain</th>
<th>Bloating</th>
<th>Antispasmodics Antiflatulents</th>
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<tr>
<td></td>
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<td>Anticholinergic/Antispasmodics TCAa/SSRIs</td>
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<tr>
<td></td>
<td></td>
<td>Loperamide Cholestyramine Psyllium Methylcellulose</td>
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<tr>
<td></td>
<td></td>
<td>Calcium polycarbophil Lactulose 70% sorbitol PEG solution</td>
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</tbody>
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Psychological Treatments for IBS

- Some patients with IBS may also benefit from:
  - Referral to a psychologist or psychiatrist
  - Hypnotherapy
  - Biofeedback
  - Psychodynamic therapy
  - Stress management/relaxation
  - Cognitive behavioral programs


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
**Placebo Response Rate in IBS**

31 controlled treatment trials 1966-98, $n=2469$

- Overall range 17-84%
- Median 52%
- Mean 55.6%
- Range 17-40%: 10 studies, $n=472$
- Range 41-60%: 8 studies, $n=557$
- Range 61-84%: 13 studies, $n=1440$

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**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

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**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

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**Physiological Distribution of 5-HT**

- CNS – 5%
- GI tract – 95%
  * enterochromaffin cells
  * neuronal

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Drossman & Thompson, Ann Intern Med., 1992

Gershon, Aliment Pharmacol Ther., 1999
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-HT_{1}: Inhibition of neurotransmitter release and increased smooth muscle contraction
  - 5-HT_{2}: Contraction of gut smooth muscle

Serotonin (5-HT) Receptors in the Gut

<table>
<thead>
<tr>
<th>Pharmacologic Action</th>
<th>5-HT_{3} Antagonists</th>
<th>5-HT_{4} Agonists</th>
</tr>
</thead>
</table>

Serotonin Agents

- **5-HT_{3} Receptor Antagonists**
  - Alosetron (Lotronex®)
  - Ondansetron (Zofran®)
  - Cilansetron

- **5-HT_{4} Receptor Agonists**
  - Cisapride (Propulsid®)
  - Prucalopride (Resolor®)
  - Tegaserod (Zelprin®)
Alosetron (Lotronex®) in IBS

- Selective 5-HT3 receptor antagonist
- Enhances jejunal water/salt absorption
- Increases colonic compliance
- Slows colonic transit
- FDA approved for women with diarrhea-predominant IBS

Alosetron (Lotronex®): 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

Alosetron (Lotronex®): Pain Relief in IBS

Camilleri et al., Lancet, 2000

Alosetron (Lotronex®): Serotonin (5-HT) and Motor Activity

Adopted from Gridner et al, Gastroenterology 1998; 115: 370
**Tegaserod (Zelnorm®)**
- 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

**Motility Disorders**
Carlo Di Lorenzo, MD
Professor of Clinical Pediatrics
Nationwide Children’s Hospital

**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
- Amitiza: Secretion at Chloride channel

**Objectives**
- To describe normal and abnormal upper and lower GI tract motility
- To discuss methodology to study gastrointestinal motility
- To discuss treatment for motility disorders
Pathophysiology of FGID

Manometry studies tell us:
- If we are dealing with a motility problem (vs emotional, sensory, parental hypervigilance, etc)
- What works and what does not
- Why it does not work (?)
- How to make it work better (directs rx)
- Whether it will ever work (prognosis)
- What organs to transplant

She has received:
- Esophageal manometry
- Antroduodenal manometry
- Colonic manometry
- Anorectal manometry

Enteric Nervous System (ENS) Comprises the Myenteric and Submucosal Plexus
Enteric Nervous System:
The “Brain-In-The-Gut” Concept

Brain-like functions of ENS
- Program library
- Feedback control
- Reflexes
- Information processing

Interneurons
- Reflexes
- Program library
- Information processing

Sensory neurons
- Muscle
- Secretory epithelium
- Blood vessels

Gut Behavior

Motor neurons
- Motility patterns
- Secretory patterns
- Circulatory patterns

ENs Contains a Limited Library of Programs for Specific Patterns of Intestinal Motor Behavior

- Postprandial program (Mixing pattern)
  - Small intestine

- Aboral power Propulsion program
  - Small and large intestine

- Physiologic ileus (Contraction absent)
  - Small and large intestine

- Emetic program (Oral power propulsion)
  - Small intestine

- Haustral program (Segmental contractions)
  - Large intestine

Enteric nervous system

Sensory, Motor, and Interneurons are Synaptically Interconnected to Form the Microcircuits of the ENS

Gut Behavior

Bidirectional Communication Between the ENS and the CNS
“The problem is in your head”

- Powerful influence of emotions and CNS on gut mucosal and motor function
  Examples: finals, big game, getting married,

- Efficacy of reassurance, behavioral modifications and relaxation techniques

Bodily changes during experimental “headache”

Colonic changes accompanying baseless fear in a healthy subject

Almy TP et al. Gastroenterology. 1950;15:95-103
**Motility: Methods & Measurements**

**Established Parameters & Techniques**
- Intraluminal pressure:
  - Manometry (stationary, ambulatory)
    - Phasic contractions: rhythmic phasic, HAPC, propulsive / nonpropulsive
  - Barostat (single, dual)
    - Tonic contractions
    - Tonic reflexes
- Myoelectric activity:
  - Electromyography
    - Slow wave, spike bursts

**Emerging Parameters & Techniques**
- Wall motion:
  - Ultrasonography, SPECT, MRI
  - Organ volumes, contractile activity, gastric accommodation
- Manometry:
  - The “SmartPill”
- Other biomechanical properties:
  - High frequency intraluminal ultrasound, impedance planimetry
- Wall tension, wall stress, wall strain

**Motor Patterns in the Gut**

**Fasting**
- Periodic motor activity with 3 sequential phases (MMC)
  - No motor activity
  - Sporadic activity
  - Regular activity
- ENS modulated by CNS

**Fed**
- Fundic relaxation
- Vagovagal reflex
- Sustained but irregular and non-periodic activity until all nutrient has left the stomach
- ENS modulated by vagal receptors
- Increase in high amplitude propagated contractions, phasic contractions & tone
- Defecation ENS + CNS

**Defecation**
- ENS + CNS
The Stomach is Divided into Three Anatomic and Two Functional Motor Regions

**Anatomic regions**
- Fundus

**Functional motor regions**
- Antrum
- Pylorus
- Lower esophageal sphincter
- Gastric reservoir
- Phasic contractions
- Antral pump
- Tonic contractions

**Gastric reservoir**
- Tonic contractions
- Antral pump
- Phasic contractions

**Onset and Rate of Gastric Emptying Varies with the Composition of the Meal**

<table>
<thead>
<tr>
<th>% Meal remaining in stomach</th>
<th>Time after meal (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid meal</td>
<td>0 20 40 60 80 100</td>
</tr>
<tr>
<td>Semi-solid meal</td>
<td>0 20 40 60 80 100</td>
</tr>
<tr>
<td>Liquid meal</td>
<td>0 20 40 60 80 100</td>
</tr>
</tbody>
</table>

**Relaxation and Increased Volume**

- Enteric nervous system
- Interneuronal circuits
- Inhibitory motor neurons
- Muscle relaxation

**Barostat = Constant Pressure**

- Pressure
  - mmHg
  - contraction
  - relaxation
- Volume
  - ml
- non-compliant balloon
Adaptive Relaxation in the Gastric Reservoir is Lost After Vagotomy

Dyspepsia
Pathophysiologic defect determines the symptom

Functional Dyspepsia

Motility:
Small Intestine
The Migrating Motor Complex (MMC) is the Small Intestinal Motility Pattern of the Interdigestive State.

Pressure recording ports on catheter

MMC activity front

Time (min)

Feeding Shifts Neural Programming from the Interdigestive Motility Pattern (MMC) to the Digestive Pattern (Segmentation)

Interdigestive

Meal Digestive

Ileum

Segmenting motility

Phase I

CNS Modulation

Asleep Stressed Awake

Why is Motility Abnormal?
Acquired Intestinal Aganglionosis and Circulating Autoantibodies without Neoplasia or Other Neural Involvement

Eosinophilic Ganglionitis

Activated mast cells in IBS

Constipation
Anorectal Manometry

- Assesses the internal and external anal sphincters, rectal sensations and expulsion patterns
- A pressure-sensitive catheter is inserted into the anorectum to measure resting and squeeze pressures of the anal canal

Balloon Distension in the Rectum Evokes Relaxation of the Internal Anal Sphincter and Contraction of the External Anal Sphincter

Biofeedback Training Defecation Disorders
Components of the Continence Apparatus

- Puborectalis
- Symphysis pubis
- Superficial external anal sphincter (EAS)
- Internal anal sphincter
- Coccyx

The Ano-Rectal Angle is Determined by the Contractile State of the Puborectalis Muscle

- Measures rate at which fecal residue moves through colon
- The patient swallows a capsule filled with radiopaque markers
- Serial abdominal radiographs are taken 120 hours later
- Hinton technique

Defecography

- Detects structural abnormalities of the rectum
- Thickened barium is instilled into the rectum
- Radiographic films are taken during defecation

Colonic Transit Study
Colonic Transit Study (Metcalf Technique)

- Ingest 24 radiopaque markers on 3 successive days
- No laxatives, enemas, or medicines that affect bowel function
- Days 4&7: abdominal plain film
- Colonic transit = markers (on day 4 and 7), normal <70 markers

Types of Prokinetics

<table>
<thead>
<tr>
<th>Types of Prokinetics</th>
<th>Dopamine-2 antagonist</th>
<th>5-HT4 antagonist</th>
<th>5-HT3 antagonist</th>
<th>Motilin Receptor agonist</th>
<th>Cholinesterase inhibitor</th>
<th>QT prolongation</th>
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<tbody>
<tr>
<td>Metoclopramide</td>
<td>+</td>
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<tr>
<td>Domperidone</td>
<td>+ +</td>
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<tr>
<td>Cisapride</td>
<td>+ +</td>
<td>+</td>
<td></td>
<td></td>
<td>++</td>
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</tr>
<tr>
<td>Erythromycin, ABT-229</td>
<td>+ +</td>
<td>+</td>
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<td>Itopride</td>
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<td>Tegaserod</td>
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FDA-Approved Treatment Options for Constipation

<table>
<thead>
<tr>
<th>Osmotic agents</th>
<th>Lactulose</th>
<th>Indicated for the treatment of constipation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyethylene glycol (PEG)</td>
<td>Polyethylene glycol (PEG)</td>
<td>Indicated for the short-term treatment of occasional constipation</td>
</tr>
</tbody>
</table>

5-HT4 Receptor Agonist

- Tegaserod*: Indicated for: Men and women < 65 years old with chronic idiopathic constipation. Women with irritable bowel syndrome with constipation. (Suspended 3/30/07, IND 2/18/07)

Chloride Channel activator

- Lubiprostone: Indicated for: Chronic idiopathic constipation in adults.


Osmotic agents

- Lactulose

Cholelithiasis

- Polyethylene glycol (PEG)

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