Visceral Pain and Irritable Bowel Syndrome

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**Learning Objectives:**

- Explain a specific body of knowledge of visceral pain associated with Irritable Bowel Syndrome and other functional diseases

- Develop an ability to use the knowledge obtained from this presentation in research and/or clinical practice

- Develop a systematic approach to critically evaluate information to add the knowledge base in medical research and/or clinical practice
Visceral pain-associated functional syndromes

- Irritable bowel syndrome (IBS)
- Interstitial cystitis (IC) a.k.a Painful Bladder Syndrome (IC/PBS)
- Chronic pelvic pain (CPP)

Functional disorders – without known organic basis
These syndromes are estimated to affect up to 15-20% of the population worldwide. Symptoms description of IC/PBS (urgency, frequency, and bladder pain generally relieved by voiding) is parallel to the description of IBS-diarrhea (IBS-D) predominance (urgency, frequency, and abdominal pain relieved by defecation).

Incidence of episodic or persistent visceral pain associated with functional disorders is 2-3x higher (IBS) or even more (IC/PBS) in women than men.
What is Irritable Bowel Syndrome (IBS)?

- About 15% of people in the developed world are believed to be affected by IBS. The first description of the condition was in 1820 while the current term "irritable bowel syndrome" came into use in 1940s.

- The cause of IBS (group of functional disorders) is unknown. Chronic abdominal complaints are without a structural or biochemical cause.

- IBS constitutes a major health problem with gastrointestinal (GI) symptoms (direct medical costs of ~ $8 billion in the US each year).

- IBS, stands in contrast to a structural disorder: unlike ulcerative colitis and Crohn's disease, which are forms of inflammatory bowel disease (IBD) it doesn't cause changes in bowel tissue.
Symptoms of IBS

• Abdominal discomfort and pain
• Bloating, mucous in stools, diarrhea, constipation, or alternating diarrhea and constipation
• Depression, anxiety or stress

• IBS can be subdivided into main types:
  – Diarrhea-predominant (IBS-D)
  – Constipation-predominant (IBS-C)
  – Alternating diarrhea and constipation (IBS-A)
  – Neither diarrhea or constipation are common (IBS-U)
  – Developed after an infectious illness (IBS-PI)

Co-morbid disorders such as anxiety, major depression, and chronic fatigue syndrome are common
Supportive symptoms of IBS

1. Fewer than 3 bowel movements a week
2. More than 3 bowel movements a day
3. Hard or lumpy stools
4. Loose or watery stools
5. Urgency
6. Feeling of incomplete bowel movement
7. Passing mucus during a bowel movement
8. Abdominal fullness, bloating or swelling

**Diarrhea-predominant IBS (IBS-D)**

One or more of 2, 4 or 6 and none of 1, 3 or 5

**Constipation-predominant IBS (IBS-C)**

One or more of 1, 3 or 5 and none of 2, 4 or 6

The primary symptoms of IBS are abdominal pain or discomfort in association with frequent diarrhea or constipation and a change in bowel habits.
IBS Symptoms: Mechanisms and Diagnosis

Constipation
Bloating

Pelvic floor dysfunction
Altered motility, secretion
Gas Retention

Diarrhea

Increased permeability
Mucosal Inflammation
Activation of sensory fibers

Pain

Prior gastroenteritis
Genetics

Irritants: ? Gluten, BA

Bacterial ecology

Neurotransmitters
Transporters

Altered sensation

Psychosocial Factors augment sensation

Data from Camilleri M. N Engl J Med. 367
Current Treatment Is Guided by Symptom-Based Diagnostic Criteria

**IBS-C**
- Fiber
- Osmotic laxatives
- Bisacodyl
- Lubiprostone
- Linaclotide

**IBS-D**
- Loperamide and alosetron for diarrhea
- Antispasmodics for colic
- Antidepressants for pain
Gut–Brain Axis: Serotonin is important in gut function

• GI disorders may be related to
  – an imbalance of serotonin in the gut
  – an improper reaction of the digestive system to serotonin
  – a faulty communication network between serotonin in the gut and the brain and spinal cord.

• Serotonin plays a major role in modulating intestinal movement and perception of pain. Helps to soften stools by releasing water.
5HT$_3$ receptors and its antagonists

- **5HT$_3$ receptors**
  - A ligand-gated cation channel
  - Present in the GI tract
  - Control sensation, contraction of intestinal muscle
  - Release of fluid into the intestines

- **5HT$_3$ antagonists**
  - Slow intestinal transit
  - Decrease intestinal secretions
  - Decrease the water content of stool
  - Diminish colonic pain
  - Melatonin retards gastric emptying through effects on vagal afferents mediated at 5HT$_3$ & play a role in visceral nociception
5HT$_4$ receptors and its agonists

- **5HT$_4$ receptors**
  - G-protein-coupled receptor
  - Present in the GI tract
  - Mediate both relaxation and contraction of circular smooth-muscle strips
  - Induces small bowel and to a lesser extent colonic fluid secretion

- **5HT$_4$ agonists**
  - Accelerate gastric emptying
  - Accelerate small and large bowel transit
  - Increase stool water content
Alosetron in IBS-D

- The first drug is approved for female patients by FDA
- Brand name is Lotronex® by Glaxo Smith Kline
- A potent and selective antagonist of the 5HT$_3$ receptors
How does Alosetron works?

• Serotonin in the intestines controls how pain is felt, contraction of intestinal muscle, and release of fluid into the intestines. An excessive release of or an excessive response to serotonin causes a pain and diarrhea.
• By blocking 5HT$_3$ receptors, alosetron reduced pain and motor responses.
Alosetron- Drug for IBS-D

- Alosetron is rapidly absorbed and extensively metabolized.
- Effective in relieving pain, normalizing bowel frequency, and reducing urgency.
- Constipation is the most common adverse effect.
- Appears to provide a modest benefit to women.
- Should be prescribed under the guidance of a specialist.
- Serious side effects and high-cost maintenance problem.
Tegaserod in IBS-C

- The first selective serotonin 5HT$_4$ receptor partial agonist approved by FDA for the treatment of abdominal pain and constipation predominant IBS patients
- Brand name is Zelnorm® by Novartis: the only agent approved in US to treat the multiple symptoms of IBS (in women only), including constipation, abdominal pain, and bloating.
How does Tegaserod work?

- The exact mechanism of tegaserod’s action is not yet understood completely.
- Tegaserod binds with high affinity at 5HT₄ receptors.
- The activation of 5HT₄ receptors in GI tract stimulates the peristaltic reflex and intestinal secretion. As a result, contractions increase and the increased contractions speed the transit of digesting food and reverse constipation.
- Reduces the sensitivity of the intestinal pain-sensing nerves and reduces pain by inhibiting visceral sensitivity.
## Peripheral Mechanism: Altered Colonic Motility

<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>Factors Involved</th>
<th>Comment</th>
</tr>
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<tbody>
<tr>
<td>Accelerated or delayed colonic transit; may be secondary to secretory mechanism</td>
<td>Neuromuscular dysfunction</td>
<td></td>
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<tr>
<td></td>
<td>Enteroendocrine cell products (eg, 5-HT, granins)</td>
<td>Affects up to 45% of patients with IBS-D; 25% of patients with IBS-C</td>
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<tr>
<td></td>
<td>Organic acids (bile acids, SCFA)</td>
<td></td>
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<tr>
<td></td>
<td>Genetic predisposition: bile acid synthesis (Klothoβ), GUCY2C mutation</td>
<td></td>
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</table>
# Peripheral Mechanism: Small Bowel and Colonic Sensing and Response

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<th>Factors Involved</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small bowel and colonic sensing and responses</td>
<td>Activation of local secretory or motor reflexes and sensory mechanisms</td>
<td>Typically associated with diarrhea, bloating, pain</td>
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</tbody>
</table>
Actions of Treatments Based on Pathophysiology

Central pain perception

- Serotonergic (5-HT agonist, 5-HT antagonist)
- Serotonin synthesis inhibitor
- μ opioid antagonist
- CRF antagonist
- Chloride channel opener
- guanyl cyclase C agonists
- IBAT inhibitor
- AST-120

Vagal nuclei

Sympathetic

S2,3,4

Altered Motility/Secretion

- Probiotics/antibiotics
- Mast cell stabilizer
- 5-ASA compounds

Altered Sensation

- Antipsychotics
- 2,3-benzodiazepine-modulator
- κ opioid agonist
- α2δ ligand
- Neurokinin antagonists
• Alosetron, 5HT₃ antagonists, appears to provide a modest benefit to women with IBS-D. Offers a new option for the treatment of IBS-D.
• Tegaserod, 5HT₄ agonists, appears to be a promising option in women with IBS-C not responding to increased dietary fiber or laxative therapy.
• Need to discover new drugs for alternating diarrhea and constipation.
• The neurohormonal control of the gut in IBS forms the basis for the most successful treatments of functional GI disorders; classical examples are 5HT₃ receptor antagonists and 5HT₄ receptor agonists.
• The greatest unmet need is in the treatment of visceral pain.
Sex Sterioids Trinity: Membrane, Cytosolic, and Nuclear Effects

Diagram: Membrane Receptor - Estrogen / Ion Channel - Intracellular Messenger - Kinase - Target Proteins (ER - 
Alternative Effects - Direct Nuclear Action - Target Genes (ERα/β - CREB)

Diagram: Posterior - Dorsal root - Dorsal root ganglion - Sensory Neuron (C-Fiber) - Spinal nerve - Nociception from Visceral Organs

Diagram: Anterior - Posterior horn - Dorsal root - Anterior horn - Ventral root - Spinal nerve - Nociception from Visceral Organs
Alternative mechanisms of action of steroids

- The rapid time course of the primary effect is too fast to be compatible with RNA synthesis or protein translation (seconds to minutes)

- Dependence (or independence) on the presence of classic ERs

- The extracellular membrane-delimited primary effect might be achieved by estrogen conjugated to membrane-impermeant molecules (E-6-BSA)
Activation and Sensitization of Primary Afferents

**ACTIVATION**

- Acid
- Mechanical
- Chemical

**Pain and Auto-sensation**

Voltage gated sodium channels

generator potentials

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Somatosensory cortex of postcentral gyrus

Ascending pathways

Thalamus

Second-order neurons

Spinal cord

First-order neurons

Primary motor area sequence

Primary sensory area sequence

Motor cortex (precentral gyrus)

Somatic sensory cortex (postcentral gyrus)

Toes

Hand

Leg

Arm

Face

Eye

Nose

Teeth

Gums

Jaw

Tongue

Pharynx
Ligand-gated Ion Channels

Na^+  K^+  Ca^{++}  Na^+

Voltage gated

Ligand gated

P2X

Acid Capsaicin Heat

VR1
Voltage-gated Ion Channels

Neurotransmitter release → Efferent Function → Afferent Function

Voltage-gated

Na⁺, K⁺, Ca⁺⁺

Heartbeat signal
G-protein Coupled Receptors

Increase excitability

Decrease excitability

PGE₂

MOR

MOR

Giα

Giβγ

AC

PLC

DAG

IP₃

Ca²⁺

Na⁺

K⁺

Ca²⁺

cAMP

PKC

PKA

VGCC (N, P/Q)

VR1

Ligand gated

Voltage gated

Acid Capsaicin Heat
Hypothesis I: Estradiol modulates nociceptive signaling associated with pelvic pain in vitro
Hypothesis II: Primary afferent neurons as site of convergence for different pelvic organs (In vivo studies):

Communication between somatic and visceral organ systems has been demonstrated. Unclear where systems converge.

Small subset of neurons may dichotomize and innervate two different visceral systems:
- lower GI system
- the female reproductive system

Is DRG a site for viscero-visceral cross-sensitization?
Methods:
Retrograde labeling of DRG (primary sensory neurons) innervating uterus and colon
Viscerally- Labeled DRG Neurons

<table>
<thead>
<tr>
<th>Levels of Spinal Cord</th>
<th>Labeled DRG neurons (%)</th>
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<tbody>
<tr>
<td>L1</td>
<td>10</td>
</tr>
<tr>
<td>L2</td>
<td>15</td>
</tr>
<tr>
<td>L3</td>
<td>10</td>
</tr>
<tr>
<td>L4</td>
<td>5</td>
</tr>
<tr>
<td>L5</td>
<td>20</td>
</tr>
<tr>
<td>L6</td>
<td>15</td>
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<td>S1</td>
<td>10</td>
</tr>
<tr>
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<td>5</td>
</tr>
<tr>
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<td>10</td>
</tr>
</tbody>
</table>

- Uterus
- Colon
- double
A subset of DRG neurons innervate both visceral organs: uterus and colon

Conclusion

- A subpopulation of DRG neurons innervate both the uterus and colon
- Sensitization may play a role in the perception of sensation and pain possibly via viscerovisceral hyperalgesia”
- Peripheral sensitization may involve:
  - Increased transduction
  - Increase in excitability (decrease in threshold)

**DRG acts as a site for cross-sensitization between different visceral organs**
Neuropathic Correlates of Visceral Pain Syndromes

**Visceral hyperalgesia**
Visceral Sensitization e.g. IBS, IS-PBS, Dysmenorrhea

**Viscero-somatic Hyperalgesia**
Referral/Neurogenic Inflammation e.g. IC/PBS with vulvodynia; dysmenorrhea/ Endo with dyspareunia

**Viscero-visceral hyperalgesia**
Referral sensitization to second viscera: IC/PBS with IBS, Endo with IC-PBS

**Viscero-Muscular Reflex**
Pelvic Floor Tension Myalgia

Given the high levels of anxiety seen in IBS patients and the overlap with motor/autonomic regulations a potential model of IBS involves a disruption of the nociceptive system.
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