Irritable Bowel Syndrome (IBS)
NP Clinical Approach

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Presenter Disclosure Information

Speakers Bureau honorarium:
• Allergan
• Merck
• Gilead
• Abbvie

Objectives

Upon completion of presentation, participant will be able to:
• Understand what defines IBS
• Understand current thinking/hypotheses of IBS pathophysiology
• Identify appropriate, individualized, efficient approach to IBS diagnosis
• Understand IBS therapy with focus on management of constituent symptoms
Background – Historical Perspective

• 1849 – (Cumming)
  “The bowels are at one time constipated, at another lax, in the same person. How the disease has two such different symptoms I do not profess to explain”

• 1892 – mucous colitis (Osler)
  “Disorder of mucorrhea and abdominal colic with a high incidence in patients with coincident psychopathology.”
    Mucous colitis, neurogenic mucous colitis, unstable colon

• 1962 – Irritable colon syndrome (Chaudhary & Truelove)
  Spastic colon, irritable colon, and nervous colon

• 1966 – Irritable bowel syndrome (IBS) (DeLor)
  “Functional GI disorder characterized by abdominal pain & altered bowel habits in absence of specific & unique organic pathology”
Background – Historical Perspective

• Past, considered diagnosis of exclusion; however, no longer considered a
diagnosis of exclusion, but it does have a broad differential diagnosis

• Long dismissed as psychosomatic condition
  • No clear etiology
  • Affects predominantly women – 70%
  • Condition not fatal

• No specific motility or structural correlates have been consistently
demonstrated; however, experts suggest use of available guidelines can
minimize testing & aid in diagnosis
  • Attitudes changing

Epidemiology

• Population-based studies estimate
  • Prevalence 10-20%
  • 10-20% seek medical care
  • Top 10 reason PCP visits
  • 20-50% GI referrals
  • Incidence is markedly different among countries.
    • Western countries, women 2-3 times more likely than men
    • India subcontinent 70-80% men
    • Predominantly females (>70% of sufferers)
  • Peak prevalence from 20 to 39 years of age.
  • More common in lower socioeconomic populations
  • Most common functional bowel disorder
  • Retrospectively: onset childhood.
  • 50% onset prior to 35 years.
    • Older 40 years does not exclude IBS - closer search for underlying etiology

IBS vs Common Disease Prevalence Rates in US

• Diabetes 3%
• Asthma 4%
• Heart disease 8%
• Hypertension 11%
• IBS 21%
Economic Costs in US

DIRECT

$1.6
To $10.5
billion

INDIRECT

≤$20
billion

TOTAL

$30
billion

74% more direct health care costs vs non IBS suffers
More medications
Require > provider visits – both GI & non GI complaints
Increased diagnostic tests
Lower work productivity & higher absenteeism

Misinformation Patient & Provider

• Abdominal pain – 29% states predominant symptom
• Misinformation
  • 15% believe IBS will turn into cancer
  • 30% believe IBS increase risk for IBD, celiac disease
  • 17% believe IBS will lead to malnutrition
• Lack of information
  • Prevalent provider belief due to anxiety (80.5%) or depression (63.2%)
  • 2/3 patients recognize IBS does not shorten life expectancy

Definition

• Chronic abdominal discomfort or pain associated with altered bowel habits (constipation, diarrhea) for at least 3 days per month in the previous 3 months, with absence of organic disease.
  • Functional GI disorder; absence of structural or biochemical abnormalities (celiac disease, IBD, GERD)
• Absence of abdominal pain excludes irritable bowel syndrome.
Chronic Idiopathic Constipation: Definition

Chronic Idiopathic Constipation (CIC)
- Defecation characterized by chronic, infrequent bowel movements (less than 3/week), difficult stool passage, or both
  - Idiopathic – unknown cause, not due to underlying medications, structural (colon cancer), or biochemical abnormalities (hypothyroidism)
  - Difficult stool passage includes straining, incomplete bowel movements (incomplete evacuation), hard/lumpy stools, prolonged time between bowel movements, need for manual removal of stool

Criteria for Diagnosis

Four bowel patterns/subtypes:
- IBS-D (diarrhea predominant)
- IBS-C (constipation predominant)
- IBS-M (mixed diarrhea & constipation)

Usefulness of subtypes debatable
- Within 1 year, 75% change subtypes, 29% switch between IBS-C & IBS-D

Diagnosis: Rome IV Criteria

- Although a number of clinical definitions have been used & defined, the Rome criteria have been the most widely used & accepted
- Symptom onset >= 6 months prior to diagnosis
- Recurrent abdominal pain, on average >= 1 day/week in the last 3 months with >= of the following
  - Related to defecation
  - Associated with a change in stool frequency
  - Associated with a change in stool form/appearance
Evolution of Rome Diagnostic Criteria

Rome Diagnostic Criteria for IBS

Rome IV criteria (2016)
- At least 3 months, with onset at least 6 months previously, of recurrent abdominal pain or discomfort associated with 2 or more of the following:
  - Relieved by defecation
  - Onset associated with a change in stool frequency
  - Onset associated with a change in stool consistency
  - Improvement with defecation
  - Onset associated with a change in frequency of stool

Rome IV criteria (1999)
- 12 weeks or more in the last 12 months of abdominal discomfort or pain with 2/3 of the following:
  - Relief by defecation
  - Associated with a change in frequency of stool
  - Associated with a change in consistency of stool

The second group of criteria included in Rome I are now considered supportive rather than mandatory in the diagnosis.

Diagnosis: Rome IV Criteria

Bristol Stool Scale

| Type 1 | Soft stool; lumps, lumps moderate (solid to liquid) |
| Type 2 | Sausage-shaped soft lumps |
| Type 3 | Like a sausage with a crack or cracked on it's surface |
| Type 4 | Like a sausage or crumbly, smooth and soft |
| Type 5 | Soft stool with clear edges (semi-formed) |
| Type 6 | Fleecy pieces with ragged edges, a flaxen stool |
| Type 7 | Watery, no solid pieces, entirely liquid |

Escola de Bristol de Consistencia de Pesc(164,575),(840,919)
Prevalence & Impact in U.S.

<table>
<thead>
<tr>
<th></th>
<th>IBS-D</th>
<th>IBS-C</th>
<th>CIC</th>
</tr>
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<tbody>
<tr>
<td>Prevalence</td>
<td>15 million adults</td>
<td>13 million adults</td>
<td>35 million adults</td>
</tr>
<tr>
<td>Average # Day/Year with Frequent/Bothersome Symptoms</td>
<td>144 days</td>
<td>135 days</td>
<td>99 days</td>
</tr>
<tr>
<td>Visits to Healthcare Providers Compared with Matched Controls</td>
<td>3 x more often</td>
<td>1.5 x more often</td>
<td>1.4 x more often</td>
</tr>
</tbody>
</table>

Comorbidities

91% patients with IBS report >/= 1 comorbidity
Average number comorbidities reported were 5 (1 mental, 4 physical)
- Anxiety
- Depression
- Back pain
- Agoraphobia
- Tension headache
- Insomnia

Etiology

- Causes remain poorly defined – not clear
- Being avidly researched
- Number of theories
Etiology - Postulated

• Threefold increase risk - 1st degree family member with IBS - genetics
• Disturbances in gastrointestinal motility
• Mucosal barrier disruption
• Visceral hypersensitivity
• Dysfunction of gut-brain axis (neurohormonal interactions between central nervous system and gut)
• Stress response with involvement of neurotransmitters.
• Reduced plasma serotonin levels – IBS-C
• Increased plasma serotonin release – IBS-D

Etiology - Postulated continued

• Post-infectious
• Food intolerance
• Small intestinal bacterial overgrowth
• Mast cell dysfunction
• Others

Comparison of Pain Thresholds

Colonic Distension  Ice Water Immersion
Transit, Motility

- Abnormal transit profiles & enhanced perception of normal motility may exist
- 1/3 may have altered colonic transit
- Delayed colonic motility may be more common with IBS-C than in healthy controls
- Similarly, accelerated colonic transit may be more common with IBS-D than in healthy controls
- Local histamine sensitization of afferent neuron causing earlier depolarization may occur

Altered GI Motility

- Distinct aberrations in small & large bowel motility
- Myoelectric activity of colon composed of background slow waves with superimposed spike potentials. Colonic dysmotility in IBS manifests as variations in slow-wave frequency & a blunted, late-peakig, postprandial response of spike potentials. IBS-D demonstrate these alterations to a greater degree than patients who are prone to IBS-C
- Small bowel dysmotility manifests in delayed meal transit (IBS-C) & in accelerated meal transit prone to diarrhea. Shorter intervals between migratory motor complexes (predominant interdigestive small bowel motor patterns)
- Current theories integrate - widespread motility aberrations & hypothesize a generalized smooth muscle hyperresponsiveness. Describe increased urinary symptoms, including frequency, urgency, nocturia, & hyperresponsiveness to methacholine challenge

Visceral Hyperalgesia

- Enhanced perception of normal motility & visceral pain
- Rectosigmoid & small bowel balloon inflation produces pain at lower volumes
- Widened dermatomal distributions of referred pain. Sensitization of intestinal afferent nociceptive pathways that synapse in dorsal horn of spinal cord provides a unifying mechanism
Comparison Pain Thresholds

Enteric Infection

- Colonic muscle hyperreactivity & neural & immunologic alterations of colon & small bowel may persist after gastroenteritis
- Psychological comorbidity independently predisposes to development of postinfectious IBS
- Psychological illness may create a proinflammatory cytokine milieu, leading to IBS through undefined mechanism after acute infection
- *Giardia lamblia* - increased IBS prevalence, as well as chronic fatigue syndrome
- *G lamblia* infection (detected by stool cysts), IBS prevalence 46.1% as long as 3 years after exposure, compared 14% in controls

Intestinal Biome Alteration

- Small bowel bacterial overgrowth has been heralded as a unifying mechanism for symptoms of bloating & distention
  - led to proposed treatments with probiotics & antibiotics.
- Fecal microbiota also differs
  - Sophisticated molecular analysis suggested alteration in patterns & contents of gut bacteria
Psychopathology

- Associations between psychiatric disturbances - not clearly defined.
- Psychological disturbances relate more frequent & debilitating illness than control populations
  - Higher incidence: panic disorder, major depression, anxiety disorder, & hypochondriasis
  - May have suicidal ideation and/or suicide attempts (IBS symptoms)
  - Clinical alertness to depression & hopelessness mandatory
  - Study: patient perception IBS trivialized
- Axis I disorder coincides with onset of GI symptoms - 77%.
- Higher prevalence physical & sexual abuse
  - Whether psychopathology incites IBS development or vice versa remains unclear.

Central Neurohormonal Mechanisms

- Abnormal glutamate activation of N- methyl-D-aspartate (NMDA) receptors, activation of nitric oxide synthetase, activation of neurokinin receptors, & induction of calcitonin gene–related peptide have been observed
- Limbic system mediation of emotion & autonomic response enhances bowel motility & reduces gastric motility
- Limbic system abnormalities, as demonstrated by positron emission tomography, have been described with IBS & major depression
- Hypothalamic-pituitary axis. Motility disturbances correspond to increase in hypothalamic corticotropin-releasing factor (CRF) production in response to stress. CRF antagonists eliminate these changes.

Microscopic Inflammation

- Documented in some patients
  - Groundbreaking: IBS previously considered to have no demonstrable pathologic alterations
- Colonic inflammation & small bowel inflammation – discovered after infectious enteritis (postinfectious IBS). Risk factors for developing postinfectious IBS:
  - Include longer duration of illness
  - The type of pathogen involved
  - Smoking
  - An absence of vomiting during the infectious illness
  - Young age
- Laparoscopic full-thickness jejunal biopsy samples revealed infiltration of lymphocytes into myenteric plexus & intraepithelial lymphocytes in one study. Neuronal degeneration of myenteric plexus was also present
- Postinfectious IBS may have increased numbers of colonic mucosal lymphocytes & enteroendocrine cells. Enteroendocrine cells in postinfectious IBS appear to secrete high levels of serotonin, increasing colonic secretion & possibly leading to diarrhea
Clinical Presentation

• Altered bowel habits:
  • Constipation - hard stools, narrow caliber, painful/in frequent defecation, & intractability to laxatives
  • Diarrhea - small volume loose stool, evacuation preceded by urgency or frequent defecation
  • Postprandial urgency - common, alternation between constipation & diarrhea
  • Characteristically, one feature generally predominates, but significant variability exists among patients

Clinical Presentation

Abdominal pain

• Pain frequently diffuse without radiation
• Common sites - lower abdomen, specifically LLQ
• Acute episodes sharp pain often superimposed on constant dull ache
• Meals may precipitate pain
• Defecation commonly improves pain but may not fully relieve it
• Pain from presumed gas pockets in splenic flexure may masquerade as anterior chest pain or LUQ abdominal pain

Clinical Presentation

Additional symptoms consistent with IBS

• Clear/white mucorrhea of noninflammatory etiology commonly reported. Epidemiologic associations with dyspepsia, heartburn, nausea, vomiting, sexual dysfunction (including dyspareunia & poor libido), & urinary frequency & urgency have been noted
• Symptoms may worsen in perimenstrual period
• Fibromyalgia common comorbidity
• Stressor-related symptoms may be revealed with careful questioning (emphasize avoidance of stressors)
Clinical Presentation

Physical examination
• Overall healthy appearance
• May be tense or anxious
• Sigmoid tenderness or palpable sigmoid cord.

Diagnostic Paradigm

• Syndrome – a collection of symptoms
• Diagnosis possible – through history of symptoms, physical exam
  • Symptoms non specific – consider alternative organic diagnoses
  • Alarm symptoms, “Red Flags”

Red Flags

Additional diagnostic screening needed for atypical presentations

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Red Flags</th>
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<tbody>
<tr>
<td>Anemia</td>
<td>Nocturnal symptoms - pain &amp; abnormal bowel function</td>
</tr>
<tr>
<td>Fever</td>
<td>Family history - GI cancer, IBD, or celiac disease</td>
</tr>
<tr>
<td>Persistent diarrhea</td>
<td>New onset symptoms - 50+ years of age</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>Palpable abdominal mass</td>
</tr>
<tr>
<td>Severe constipation</td>
<td>Severe of progressively worsening symptoms</td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
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<tr>
<td>Anorexia, persistent</td>
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</table>
Diagnosis

- Comprehensive history, physical examination, & tailored laboratory & radiographic studies can establish diagnosis in most
- ACG (American College of Gastroenterologists) does not recommend laboratory testing or diagnostic imaging in <50 years with typical IBS symptoms & without “alarm features”
  - Weight loss
  - Iron deficiency anemia
  - Family history GI illnesses (IBD, celiac sprue, colorectal cancer)
  - Rectal bleeding & nocturnal symptoms - alarm features, not specific for organic disease.
  - IBS-D or IBS-M - serologic testing for celiac sprue.
  - 50 years & older - more extensive testing, including colonoscopy

ACG Test Recommendation: IBS No Alarm Features

- Routine laboratory tests: CBC, CMP, TSH, stool O&P
- Abdominal imaging – not recommended
- Serologic testing celiac disease (IBS-D/M) – strongly consider
- Lactose breath tests – selected cases
- Colonoscopy with biopsy – IBD-D
  - Recommended is >/= 50 yo
  - Refractory diarrhea

ACG=American College of Gastroenterology

History-Specific Examinations

Stool examinations- diarrhea
Microbiologic studies to consider:
  - Ova & parasites
  - Giardia antigen
  - Enteric pathogens
  - Leukocytes
  - Clostridium difficile toxin
  - H. Pylori
History-Specific Examinations

- Hydrogen breath test - exclude bacterial overgrowth (IBS-D)
  - screen for lactose and/or fructose intolerance.
- Tissue transglutaminase antibody testing & small bowel biopsy (IBS-D)
  - diagnose celiac disease.
- Serum calcium testing - hyperparathyroidism.
- Erythrocyte sedimentation rate & C-reactive protein measurement
  - nonspecific screening tests for inflammation.

History-Specific Imaging Studies

- Gallbladder ultrasonography
  - considered with recurrent dyspepsia or characteristic postprandial pain.
- Abdominal computed tomography (CT)
  - screen for tumors, obstruction, & pancreatic disease if diagnostic possibilities.
- CT & magnetic resonance (MR) enterography or wireless capsule endoscopy
  - red flags to suggest enteritis (small bowel inflammation) or tumor.
- Colonoscopy
  - alarm symptoms present & otherwise qualify for screening colonoscopy.

History-Specific Procedures

- Anal manometry
  - reveal spastic response to rectal distention or other problems
- Esophagogastroduodenoscopy with biopsy
  - for persistent dyspepsia, weight loss, malabsorption, or if celiac disease is in question
Differential Diagnosis

- **Gastrointestinal**
  - Colorectal cancer
  - Diverticular disease
  - Inflammatory bowel disease
  - Malabsorption—Celiac disease
  - Microscopic colitis

- **Gynecologic**
  - Ovarian cancer
  - Endometriosis

- **Drug**
  - Opiates
  - Anticholinergics
  - Antidepressants

- **Infection**
  - Giardiasis
  - Amebiasis
  - C. difficile

- **Metabolic/Endocrine**
  - Hypothyroidism
  - Diabetes

- **Neurologic**
  - Parkinson disease
  - Multiple sclerosis
  - Autonomic neuropaathy

- **Psychological disorders**
  - Pain disorder
  - Depression

- **Dietary factors**
  - Lactose
  - Gluten
  - Other FODMAPS

- **Other**
  - Amyloidosis
  - Scleroderma

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**IBS Management**

**American College of Gastroenterology (ACG) position statement**

- addressing non-gastrointestinal symptoms/comorbidities to improve health-related quality of life
- to reduce symptom severity
- evidence considered in position statement was insufficient to recommend exclusion diets or food allergy testing

Successful management relies on

- strong patient-provider relationship
- Reassure - absence of an organic pathology indicates a normal life expectancy
- emphasize - expected chronicity of symptoms with periodic exacerbations
- teach to identify stressors & avoidance techniques
Management – Diet

• Diet is #1 topic of interest (by patient)
• 60% report symptoms worsen after meals
• Studying diet is quite challenging
• True food allergies – very rare
• General recommendations: diet tailored to individual

Management

• Fiber supplementation may improve symptoms of constipation & diarrhea
• Polycarbophil compounds (Citrucel, FiberCon) may produce less flatulence than psyllium compounds (Metamucil)
• Cochrane systematic review found no benefit of fiber/bulking agents on symptoms or global assessment

Management

• Dietary manipulation
  • Several different diets have been proposed
  • Diets low in FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) hold particular interest in reducing symptoms of irritable bowel syndrome
• Probiotics
  • unclear for which patients probiotics are helpful, and in what form, dose, combination, or strain
  • One meta-analysis - *Bifidobacterium infantis* may help alleviate some symptoms
  • Systematic review & meta-analysis - 43 articles on probiotics & showed helped relieve pain, bloating, and gas; however, again, it remains unknown which probiotic is best.
FODMAPs - Fermentable Oligo- Di- Monosaccharides And Polyols

<table>
<thead>
<tr>
<th>FODMAP</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excess Fructose</td>
<td>Honey, apples, pears, peaches, mangos, fruit juice, dried fruit</td>
</tr>
<tr>
<td>Lactose</td>
<td>Milk, ice cream, cheese, whey, curd</td>
</tr>
<tr>
<td>Fructans</td>
<td>Wheat (large amounts), rye (large amounts), onions, leeks, zucchini</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>Apricots, peaches, artificial sweeteners and gums</td>
</tr>
<tr>
<td>Raffinose</td>
<td>Lentils, cabbage, Brussels sprouts, asparagus, green beans, legumes</td>
</tr>
</tbody>
</table>

Management

- **Probiotics**
  - Unclear for which patients probiotics are helpful, and in what form, dose, combination, or strain
  - One meta-analysis - *Bifidobacterium infantis* may help alleviate some symptoms
  - Systematic review & meta-analysis - 43 articles on probiotics & showed helped relieve pain, bloating, and gas; however, again, it remains unknown which probiotic is best.

Management - Psychological Therapy

- ACG position statement - psychological interventions, cognitive behavioral therapy, dynamic psychotherapy, & hypnotherapy, are more effective than placebo
  - Relaxation therapy was no more effective than usual care
  - Cochrane systematic review - antidepressants improved both symptoms & global assessment scores compared with placebo. Selective serotonin reuptake inhibitors (SSRIs) & tricyclic antidepressants were - effective in subgroup analyses
  - Consider psychiatric referral
Management

• Evidence mixed regarding long-term improvement in GI symptoms with successful treatment of psychiatric comorbidities
• ACG (American College of Gastroenterology) concluded the following:
  • Psychological interventions, cognitive-behavioral therapy, dynamic psychotherapy, & hypnotherapy are more effective than placebo
  • Relaxation therapy is no more effective than usual care

Management

Long-term Monitoring
• Frequent visits - enhance patient-provider relationship
  • especially recently diagnosed.
• Visits less frequent as patients are educated & reassured.

Patient Education & Support

• Providing education and options for treatment
• Ensuring treatment adherence
• Setting patient expectations
• Managing medication side effects
IBS Pathophysiology - Multifactorial

- Altered Secretion
- Visceral Hypersensitivity
- Altered GI Motility

No single treatment for all patients

Management

Pharmacologic agents – examples:

- Anticholinergics (dicyclomine, hyoscyamine)
- Antidiarrheals (diphenoxylate, loperamide)
- Tricyclic antidepressants (imipramine, amitriptyline)
- Prokinetics
- Bulk-forming laxatives
- Serotonin receptor antagonists (alostron)
- Chloride channel activators (lubiprostone)
- Guanylate cyclase C (GC-C) agonists (linaclotide)
- Antispasmodics (e.g., peppermint oil, pinaverium, trimebutine, cinetirium/decyldine)
- Rifaximin
### IBS – D Management Options

<table>
<thead>
<tr>
<th>RX Treatments</th>
<th>Pharmacologic Class</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eluxadoline – Viberzi</td>
<td>Mixed opioid receptor modulator</td>
<td>Adults - approved</td>
</tr>
<tr>
<td>Diphenoxylate + atropine (Lomotil)</td>
<td>Mu- opioid receptor and antimuscarinic</td>
<td>Adjunctive therapy</td>
</tr>
<tr>
<td>Hyoscyamine (Levsin)</td>
<td>Antispasmodic</td>
<td>Adjunctive therapy</td>
</tr>
<tr>
<td>Alosetron (Lotronex)</td>
<td>Selective serotonin 5-HT3 antagonist</td>
<td>Adults - approved</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OTC Treatments</th>
<th>Pharmacologic Class</th>
<th>Approved Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loperamide (Imodium A-D)</td>
<td>Mu- opioid receptor antagonist</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Bismuth subsalicylate (Pepto Bismol)</td>
<td>Antibacterial, anti-secretory, anti-inflammatory</td>
<td>Diarrhea</td>
</tr>
</tbody>
</table>

### IBS – C Management Options

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<tr>
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<tbody>
<tr>
<td>Linaclotide (Linzess)</td>
<td>GC-C agonist</td>
<td>Adults</td>
</tr>
<tr>
<td>Lubiprostone (Amitiza)</td>
<td>Chloride channel activator</td>
<td>Adult females (CIC – adult males &amp; females)</td>
</tr>
<tr>
<td>Lactulose (Enulose)</td>
<td>Osmotic laxative</td>
<td>Constipation/chronic constipation</td>
</tr>
<tr>
<td>Polyethylene glycol (PEG)</td>
<td>Osmotic laxative</td>
<td>Occasional constipation</td>
</tr>
<tr>
<td>Psyllium (Metamucil)</td>
<td>Bulk forming laxative</td>
<td>Occasional constipation</td>
</tr>
<tr>
<td>Bisacodyl (Dulcolax)</td>
<td>Stimulant laxative</td>
<td></td>
</tr>
<tr>
<td>Dosusate (Colace)</td>
<td>Stool softener laxative</td>
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### Medications

**Class Summary – IBS-C**
- **Lubiprostone (Amitiza)**
  - Activates chloride channels on apical part of small bowel epithelium
  - Chloride ions secreted & sodium & water passively diffuse into lumen to maintain isotonicity
  - IBS-C & CIC
- **Alosetron (Lotronex)**
  - 5-HT3 receptor antagonist
  - Potent & selective antagonism of serotonin 5-HT3 receptor type. Receptors extensively located on enteric neurons of GI tract, & stimulation causes hypersensitivity & hyperactivity of intestine
  - Indicated only for female with severe IBS-D symptoms (generally lasting >6 months), had anatomic or biochemical abnormality of GI tract excluded, & have not responded adequately to conventional therapy
  - Limiting use – severely affected population - intended to maximize benefit-to-risk ratio
  - Previously removed US market - reintroduced with restrictions 6/7/2002. Restrictions are because of reports of severe complications, including some that resulted in hospitalization & surgery, or death. Providers must be enrolled in Prescribing Program
- **Linaclotide (Linzess)**
  - GC-C agonist; activation of guanylate cyclase receptors in intestinal neurons leads to increased cyclic guanosine monophosphate (cGMP), anion secretion, fluid secretion, & intestinal transit. Appears to work locally rather than systemically, activates chloride channels in intestinal epithelial cells to increase intestinal fluid output
  - Adults male & female
Medications

Class Summary – IBS-D

• **Fluxedolone (Viberzi)**
  - Mu opioid receptor agonist. Also a delta opioid receptor antagonist & a kappa opioid receptor agonist - reducing incidence of constipation that can occur with unopposed mu opioid receptor agonists
  - IBS-D adult male and female

Medications

Anticholinergics

Class Summary

• Antispasmodics - inhibit intestinal smooth-muscle depolarization at muscarinic receptor. Relieve symptoms of intestinal spasms

- **Dicyclomine hydrochloride (Bentyl)**
  - Blocks action of acetylcholine at parasympathetic sites in secretory glands, smooth muscle, & CNS
  - Decreases fecal urgency & pain
  - Diarrhea-predominant symptoms
  - Adverse effects dose dependent

- **Hyoscyamine sulfate (Levsin)**
  - Blocks action of acetylcholine at parasympathetic sites in smooth muscle, secretory glands, & CNS
  - Antispasmodic effects.
  - Decreases fecal urgency & pain

Medications

Antidiarrheals

Class Summary

• Nonabsorbable synthetic opioids
  - Prolong GI transit time & decrease secretion via peripheral µ-opioid receptors
  - Reduce visceral nociception via afferent pathway inhibition

- **Diphenoxylate hydrochloride 2.5 mg with atropine sulfate 0.025 mg (Lomotil)**
  - Formula of 2.5 mg diphenoxylate (constipating meperidine congener) and 0.025 mg atropine to discourage abuse
  - Inhibits excessive GI propulsion & motility, may exacerbate constipation

- **Loperamide (Imodium)**
  - OTC acts on intestinal muscles to inhibit peristalsis & slow intestinal motility
  - Prolongs movement of electrolytes & fluid through bowel & increases viscosity & loss of fluids & electrolytes
  - Improves stool frequency & consistency, reduces abdominal pain & fecal urgency, may exacerbate constipation
Medications

**Antidiarrheals**
Class Summary
- **Loperamide (Imodium)**
- ACG position statement
  - antidiarrheal agent loperamide effectively reduced stool frequency & improved stool consistency, but did not relieve pain, bloating, or other global IBS symptoms

**Tricyclic Antidepressants**
Class Summary
- Both antidepressive & analgesic properties
- Imipramine & amitriptyline efficacious
- Use of tricyclic antidepressants - off label
  - **Imipramine (Tofranil)**
    - Increases pain threshold in gut, providing a visceral analgesic effect
    - Prolongs oral-cecal transit time, reduces abdominal pain, mucorrhea, & stool frequency; & increases global well-being variably
    - Effective - doses subtherapeutic for antidepressive actions, suggesting an independent mechanism of action in this disorder
  - **Amitriptyline (Elavil)**
    - Provides visceral analgesic effect at doses subtherapeutic for antidepressive actions.
    - Prolongs oral-cecal transit time, reduces abdominal pain, mucorrhea, & stool frequency, & increases global well-being variably

**Antibiotics**
Class Summary
- May play role by preventing overgrowth of intestinal bacteria
  - **Rifaximin (Xifaxan)**
    - Semisynthetic derivative of rifampin & acts by binding to beta-subunit of bacterial DNA-dependent RNA polymerase, blocking one of the steps in transcription
    - Results in inhibition of bacterial protein synthesis & consequently inhibits growth of bacteria
    - Exact mechanism of action unknown
    - Thought related to changes in bacterial content in GI tract & reduction of gas.
    - Indicated - IBS-D adult male & female
Medications
Bulk-Forming Laxatives
Class Summary
• Natural & semi-synthetic hydrophilic polysaccharides & cellulose derivatives
  • Dissolve or swell in intestinal fluid, forming emollient gels - facilitate passage of intestinal contents & stimulate peristalsis
• May improve symptoms - constipation & diarrhea - use is controversial
• Methylcellulose (CitruCel)
  Promotes bowel evacuation - forming a viscous liquid & promoting peristalsis
• Psyllium (Metamucil, Fiberall, Reguloid, Konsyl)
  Promotes bowel evacuation - forming a viscous liquid & promoting peristalsis

Non-Traditional Remedies
• Chinese Herbal Medicine (CHM)
  • 116 pts randomized to CHM did better than pts receiving placebo
• Peppermint Oil
  • Relaxation of GI smooth muscle
  • Meta-analysis showed significant symptom improvement
• Acupuncture
• Probiotics
• Others

Patient Education
• Cornerstone of successful treatment
• Teach to identify stressors & to develop avoidance techniques
• Some successfully manage symptoms with dietary triggers
Positive Diagnosis

- Identify abdominal pain as dominant symptom with altered bowel function
- Look for “red flags”
- Perform diagnostic tests/physical exam to rule out organic disease
- Make/confirm diagnosis
- Initiate treatment program as part of diagnostic approach
- Follow up in 3 to 6 weeks

Symptom-Based Approach

**IBS Symptoms**
- Meets criteria, no alarm features – make diagnosis of IBD
- Symptomatic treatment for predominant symptoms
- Assess response to treatment
  - Good response – continue RX
  - Poor response - reassess

**Alarm Features**
- Does not meet criteria - alarm features - look for alternative diagnosis

Prognosis

- Chronic relapsing disorder characterized
  - recurrent symptoms of variable severity
  - Life expectancy remains similar to general population.
- Knowledge - help allay undue fears as disease waxes & wanes
- Does not increase mortality or risk of IBD or cancer
- Increased risk of ectopic pregnancy & miscarriage, but not stillbirth
  - Cause/reasons unknown
  - IBS vs medications?
- Principal associated physical morbidities
  - abdominal pain & lifestyle modifications secondary to altered bowel habits
  - Work absenteeism - lost wages
Overview - Practice Essentials

- Chronic functional medical condition characterized
  - abdominal pain
  - diarrhea
  - constipation
  - bloating
  - passage of mucus
  - feelings of incomplete evacuation
- Precise etiology unknown
- Treatment focused on relieving symptoms rather than "curing disease"

Overview - Practice Essentials

- Although complain symptoms after eating, true food allergies uncommon
- Specific therapies - determined by individual symptoms
- Life-style modifications & possible alternative therapies may relieve symptoms
- Surgery - NO Role in treatment

Overview - Practice Essentials

- IBS highly prevalent functional bowel disorder
  - Tremendous burden due to its pervasive negative impact on the physical, social, and economic well-being of affected individuals
- Diagnosis based upon a thorough clinical history & physical examination
  - application of Rome IV criteria
- Treatment options: pharmacologic & non pharmacologic strategies
  - demonstrated efficacy at reducing symptoms and improving patient QOL
- Long term management: individualized
  - Include education & support - foster patient understanding, ensure treatment adherence & guide therapeutic expectations
Concluding Statement

• IBS is a benign condition without benign effects
• Keep an open mind while managing IBS

Thank you for interest!

Questions?