# ADVANCING GI PATIENT CARE 2022

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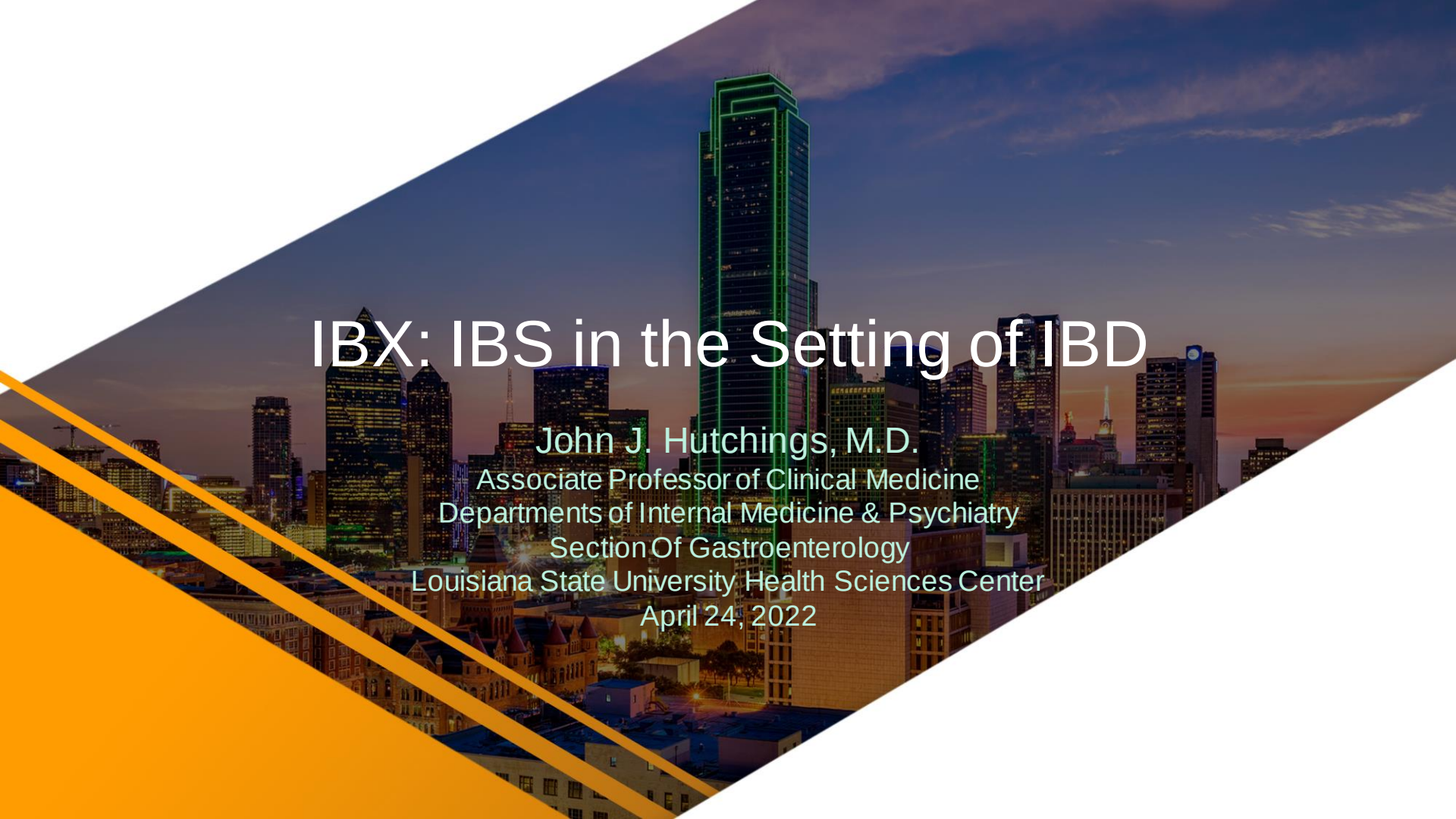

# IBX: IBS in the Setting of IBD

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# Disclosures

**John J. Hutchings, MD**

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# IBX: IBS and IBD

- IBD and IBS are often confused for one another as these entities share many clinical features in common
- Both conditions are characterized by chronic remitting and relapsing courses and can impact significantly on patients' quality of life and social activities
- The etiologies of both diseases are obscure and likely multi-factorial
- Both conditions appearing to be subject to exacerbations mediated by psychological, environmental, and genetic components as well as derangements of the gut microbiota and likely other unknown factors [1]

[1] Quigley EMM et al. Overlapping irritable bowel syndrome and inflammatory bowel disease: less to this than meets the eye? *Ther Adv Gastroenterol.* 2016;9:199–212.

# By the Numbers

- The prevalence of IBD is estimated to be between 130 -240/ 100,000 people [2]
- IBS is common in the general population with an estimated prevalence somewhere between 10% and 35% [3]
- Just based on the frequency of IBS found in the general population, some patients with IBD likely will experience IBS-like symptoms
- Post-IBD IBS was first reported in 1983 and documented IBS-like symptoms in 33% of patients with chronic Ulcerative Colitis in remission [4].

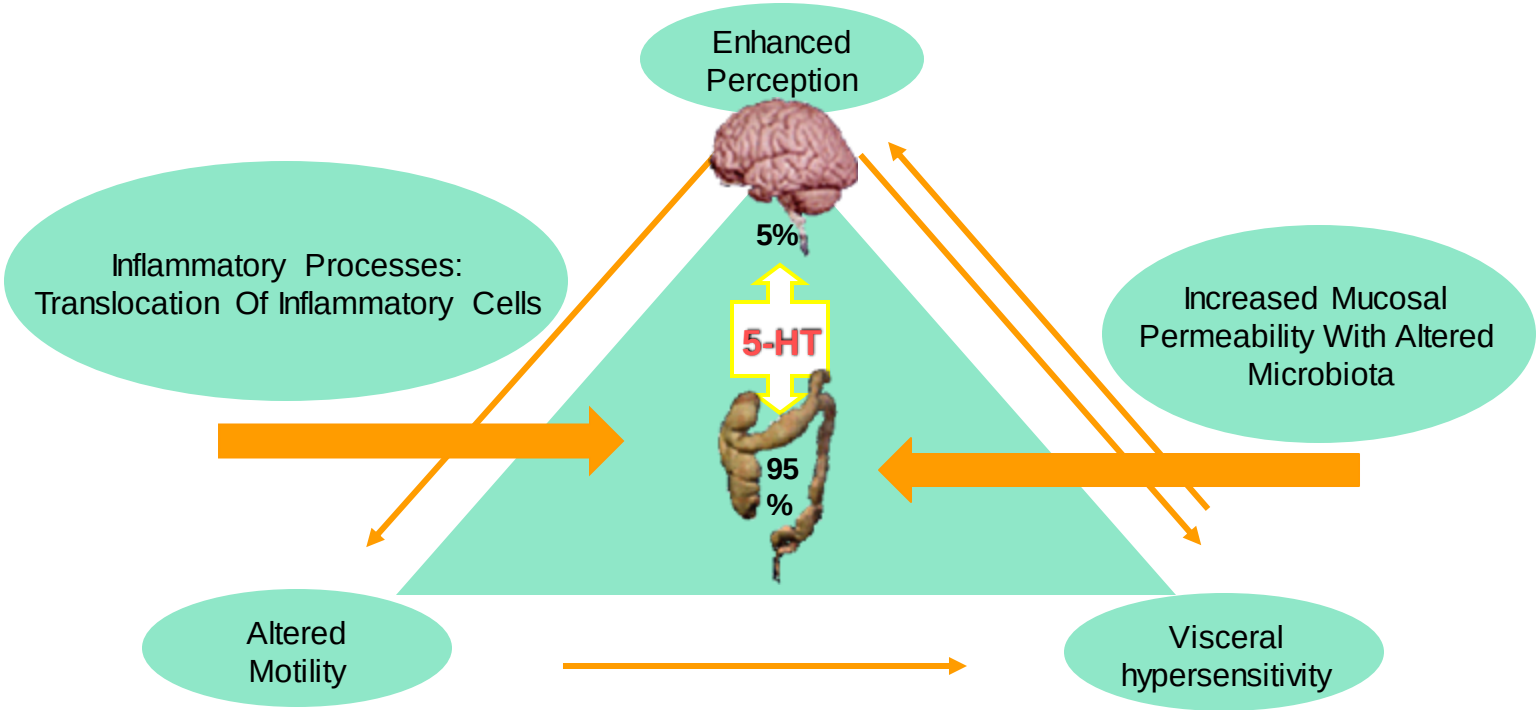
[2] Loftus CG, Loftus EV Jr, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940– 2000. *Inflamm Bowel Dis*. 2007;13:254–261; [3] Lovell RM et al. Ford AC. Global prevalence of, and risk factors for, irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol*. 2012;10:712–721; [4] Isgar B, Harman M, Kaye M, et al. Symptoms of irritable bowel syndrome in ulcerative colitis in remission. *Gut*. 1983;24:190–192.

# A Double Whammy

- A meta-analysis of 13 studies incorporating 1,703 patients calculated the prevalence of post-IBD IBS to be 35% and IBS symptoms were more frequent in patients with Crohn's disease than Ulcerative Colitis [5]
- Post-IBD IBS occurred regardless of the IBD disease type, the nature and intensity of IBD treatment modalities, and the duration of the IBD remission [6]
- Both IBD and IBS impart considerable stress, incur significant healthcare resource utilization and greatly impair the quality of life and social activities of affected patients
- Patients with post-IBD IBS appear to have more severe GI symptoms, psychological disturbances, and reduced quality of life compared to patients without IBS symptoms in the setting of IBD in remission

[5] Halpin S, Ford A, et al. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. *AJG*. 2012;107:1474–1482; [6] Berrill J, Green J, Hood K, et al. Symptoms of irritable bowel syndrome in patients with inflammatory bowel disease: examining the role of sub clinical inflammation and the impact on clinical assessment of disease activity. *Aliment Pharmacol Ther*. 2013;38:44–51.

# Post-IBD IBS: The Pathophysiologic Model




Adapted from Camilleri and Choi, *Aliment Pharmacol Ther.* 1997; 11:3.

# The BIG Clinical Question

When an IBD patient has persisting symptoms and no detectable evidence of inflammation; is this coincident IBS, IBS triggered by IBD or a subtle level of IBD activity unrecognized by available laboratory or imaging methods?

# IBD or IBS: SO How Do We Know?

- Recently developed and now widely available methodologies that detect low levels of inflammatory activity have proven of great value
- Markers of inflammation such as levels of highly sensitive C-reactive protein in the circulation, of lactoferrin in feces or levels of the pro-inflammatory cytokine tumour necrosis factor-α (TNF-α), as well as numbers of intra-epithelial lymphocytes (IELs) in cecal mucosal biopsies, levels of nitric oxide in rectal biopsies and the response of cultured mucosal biopsies to lipopolysaccharide have also helped to define the IBD patient with ongoing activity.
- The fecal level of **calprotectin** has proven to be a very sensitive measure of disease activity in IBD and its use in the IBD patient with IBS symptoms has revealed that many have active, if subclinical, activity of their IBD

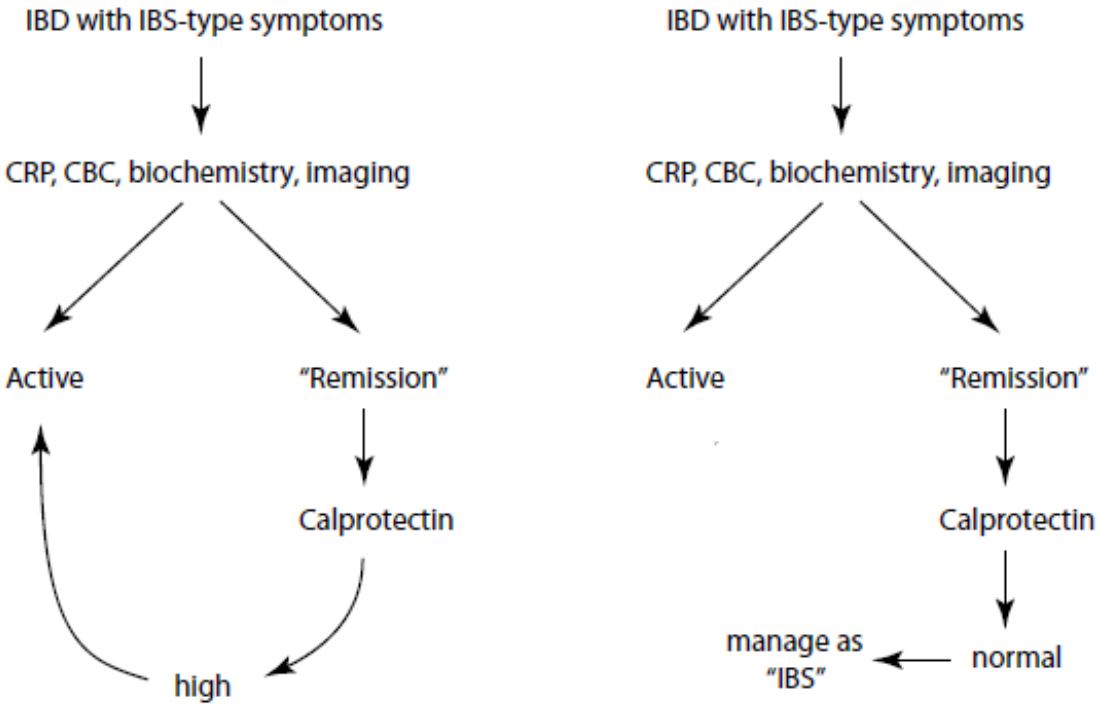
[1] Quigley EMM et al. Overlapping irritable bowel syndrome and inflammatory bowel disease: less to this than meets the eye? *Ther Adv Gastroenterol*. 2016;9:199–212.

# Cutoffs: Trade Offs Between Sensitivity and Specificity

- A cutoff value of ≤250 µg/g predicts endoscopic remission [Crohn's Disease index of Severity (CDEIS) ≤3] with 94.1% sensitivity and 62.2% specificity [positive predictive value (PPV) 48.5%, negative predictive value (NPV) 96.6%] in CD
- Similarly, in UC, a fecal calprotectin >250 µg/g gave a sensitivity of 71.0% and a specificity of 100.0% (PPV 100.0%, NPV 47.1%) for active mucosal disease (Mayo score >0)
- Based on two meta-analyses, the probability of an individual with IBS with a fecal calprotectin level of ≤40-50 µg/g harboring IBD was ≤1%.
- Jelsness-Jorgensen and colleagues suggested a cutoff of <100 µg/g provided optimal differentiation between IBS and IBD [7]
- A gray area exists between 50 µg/g which is reliably indicative of absolutely no inflammatory activity and a higher level (100 µg/g or 250 µg/g ) which indicates active IBD

[1] Quigley EMM et al. Overlapping irritable bowel syndrome and inflammatory bowel disease: less to this than meets the eye? *Ther Adv Gastroenterol*. 2016;9:199–212; [7] Jelsness-Jorgensen, L., Bernklev T., and Moum B., et al. Calprotectin is a useful tool in distinguishing coexisting irritable bowel-like symptoms from that of occult inflammation among inflammatory bowel disease patients in remission. *Gastroenterol Res Pract*. 2013: 620707.

# Flow With Me




[1] Quigley EMM et al. Overlapping irritable bowel syndrome and inflammatory bowel disease: less to this than meets the eye? *Ther Adv Gastroenterol*. 2016;9:199–212.

# Comorbidities Reported By Patients With IBS

- According to a study on the relationship of IBS with other medical factors, what is the average TOTAL number of mental and physical co-morbidities reported by patients with IBS?

Two

Three

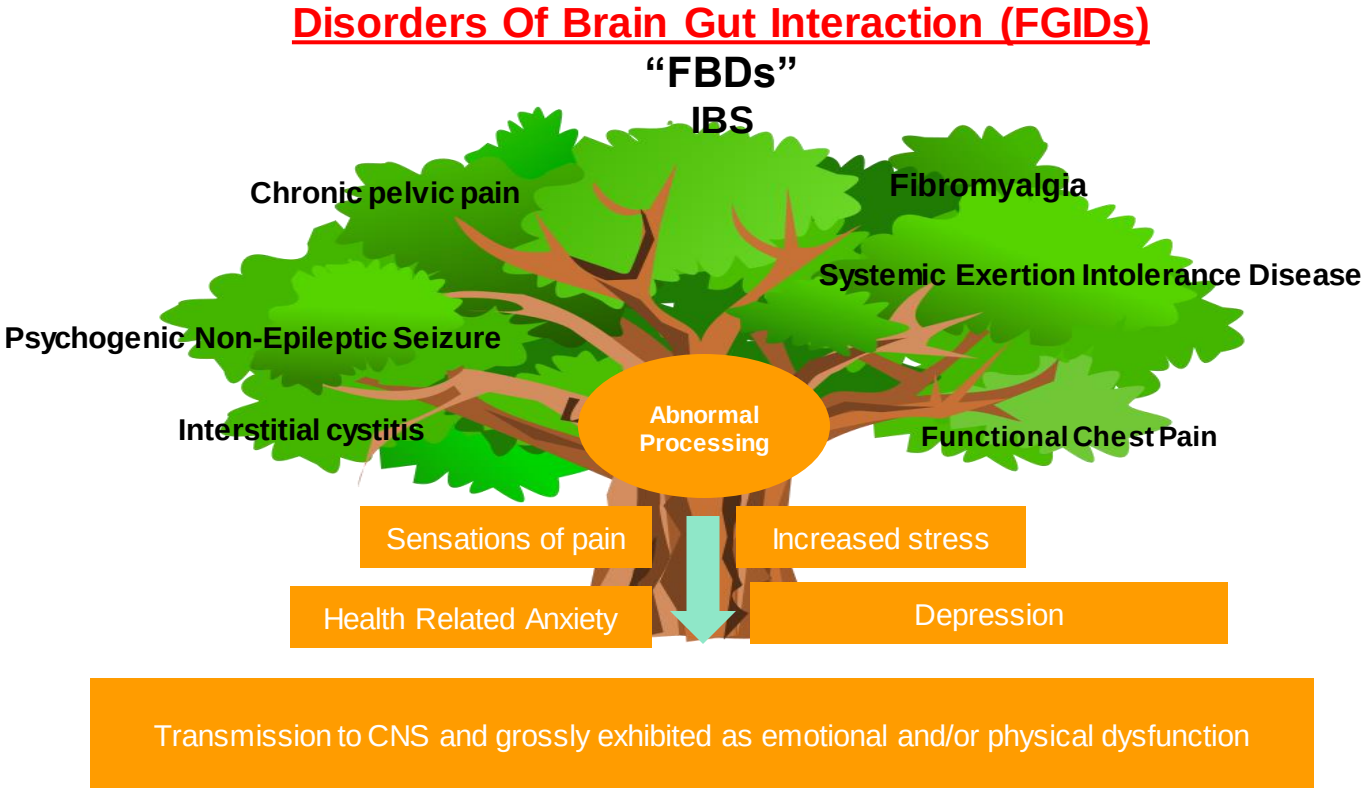
Five

# The Answer Is…

- The average number of comorbidities reported by patients with IBS is **FIVE**
  - 1 mental (predominantly health related anxiety)
  - 4 physical
- Of the comorbidities reported anxiety, depression, back pain, agoraphobia, headache, and insomnia were associated with greater illness and symptom burden
- Both mental and physical comorbidities are common among patients with IBS with more than 90% of patients reporting having one or more comorbidity [8]

[8] Lackner JM et al. *Clin Gastroenterol Hepatol*. 2013; 11(9): 1147-1157.

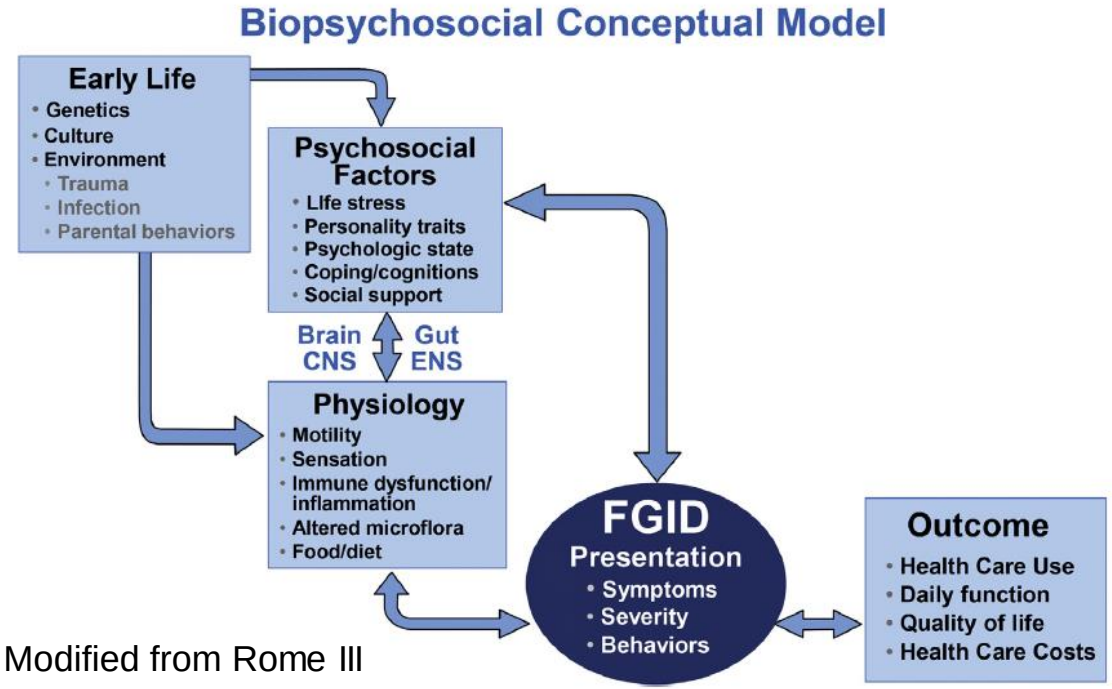
# The Tree of Functional Dysfunction



# The Evolving Definition of FGIDs

- Formally, FGIDs were defined as chronic and recurrent symptoms of the gastrointestinal (GI) tract without detectable structural or biochemical abnormalities
- Recently the FGIDs have been redefined as “disorders of gastrointestinal functioning or “disorders of the gut-brain interaction”
- There has been an intentional removal of the term 'functional' when it is not needed
- Disorders are now classified by gastrointestinal symptoms related to any combination of: motility disturbance; visceral hypersensitivity; altered mucosal and immune function; altered gut microbiota; and altered central nervous system (CNS) processing

# The Biopsychosocial Model




Modified from Rome III

[9] Engel G.L. et al. The need for a new medical model: a challenge for biomedicine. *Science.* 1977; 196: 129–136; [10] Drossman D.A. et al. The functional gastrointestinal disorders and the Rome III process. in: D.A. Drossman, E. Corazziari, M. Delvaux, (Eds.*) Rome III: the functional gastrointestinal disorders. 3rd ed.* Degnon Associates, Inc, McLean, VA; 2006: 1–29.

# Current Treatment Strategies for DGBIs

**Non-Pharmacologic**

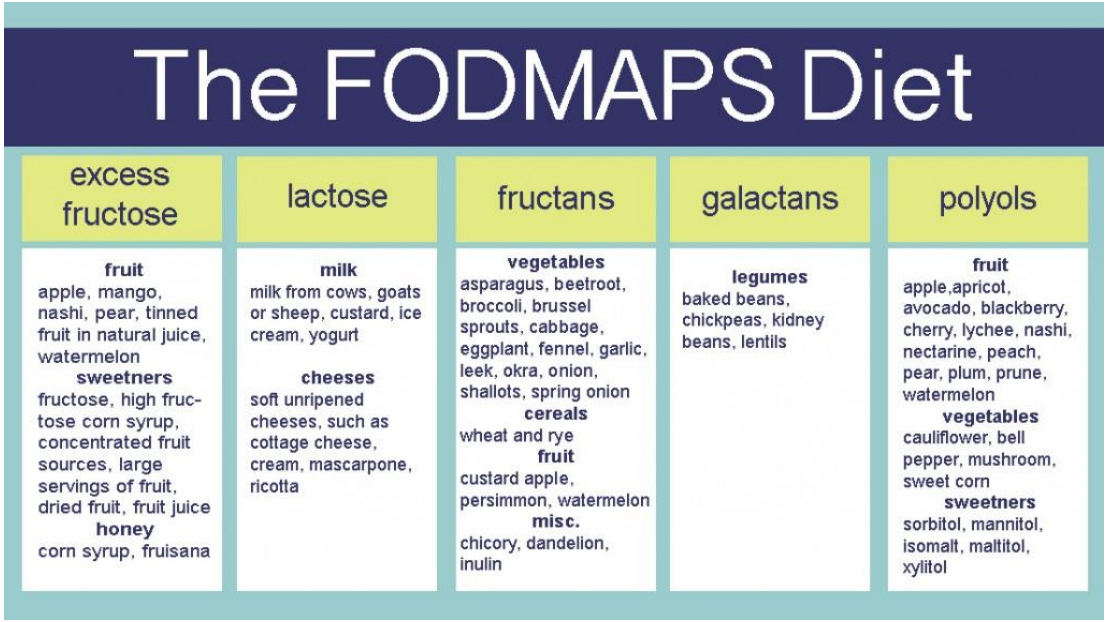
- Education And Reassurance
- Dietary Advice (FODMAPS/Fiber)
- Lifestyle Modification
- Behavioral Modification & Therapy

**Pharmacologic**

- Antispasmodic / Anticholinergic
- Anti-Diarrheal
- Laxatives
- Neuromodulators (Antidepressants)

# Just Really Fun to Say

# You Are What You Eat




- A recent study suggests that eosinophilic colopathy occurs in some post-IBD IBS-D patients and they responded to a GI-hypoallergenic diet and budesonide therapy [11]

[11] M Tozlu, B Cash, M Younes & A Ertan, et al. Dilemma in post-IBD patients with IBS-D symptoms: *A 2020 overview, Expert Review of Gastroenterology & Hepatology.* 2021. 15:1, 5-8.

# The Armamentarium

Table. Summary of Therapies for Irritable Bowel Syndrome[a]

| Treatment | Quality of Evidence | Treatment Benefits | Most Common Adverse Events |
|---|---|---|---|
| **Over-the-Counter** | | | |
| Fiber: psyllium | Moderate | Best suited for IBS-C | Bloating, gas |
| Laxatives: polyethylene glycol | Very low | Beneficial for constipation but not global symptoms or pain in IBS-C | Bloating, cramping, diarrhea |
| Antidiarrheals: loperamide | Very low | Beneficial for diarrhea but not global symptoms or pain in IBS-D | Constipation |
| Probiotics | Low | Possible benefits for global symptoms, bloating, and gas as a class but unable to recommend specific probiotics | Similar to placebo |
| Antispasmodics: peppermint oil | Moderate | Benefits for global symptoms and cramping | GERD, constipation |
| **Prescription** | | | |
| Antidepressants: TCAs, SSRIs, SNRIs | High | TCAs and SSRIs improve global symptoms and pain; leverage adverse effects to choose TCAs for IBS-D patients and SSRIs for IBS-C patients | Dry eyes/mouth, sedation, constipation, or diarrhea |
| Antispasmodics | Low | Some drugs offer benefits for global symptoms and pain | Dry eyes/mouth, sedation, constipation |
| Prosecretory agents | | | |
| Linaclotide | High | Improves global, abdominal, and constipation symptoms in IBS-C | Diarrhea |
| Lubiprostone | Moderate | Improves global, abdominal, and constipation symptoms in IBS-C | Nausea, diarrhea |
| Antibiotics: rifaximin | Moderate | Improves global symptoms, pain, and bloating in nonconstipated IBS patients | Similar to placebo |
| 5-$HT_3$ receptor antagonists: alosetron | Moderate | Improves global, abdominal, and diarrhea symptoms in women with severe IBS-D | Constipation, rare ischemic colitis |
| **Other Therapies** | | | |
| Psychological/behavioral therapy | Very low | Benefits for global IBS symptoms in all subgroups | Similar to placebo |

[12] Chey WD, Kurlander J, Eswaran S, et al. Irritable Bowel Syndrome A Clinical Review. *JAMA*. 2015;313(9):949-958. doi:10.1001/jama.2015.0954.

# Tricyclic Antidepressants (TCAs)

- Used in IBS for modulation of hyperalgesia
- Dose for hyperalgesia is typically lower than the dose for depression
- TCAs modulate activity in pain centers in the CNS
- TCAS are anti-cholinergic agents and can induce constipation

| Neuromodulator | NE | 5-HT | ACh | $H_1$ |
|---|---|---|---|---|
| Amitriptyline (Elavil) (3) | + | ++ | +++ | ++ |
| Amoxapine (Asendin) (2) | ++ | + | + | + |
| Clomipramine (Anafranil) (3) | ++ | +++ | + | + |
| Desipramine (Norpramin) (2) | +++ | + | + | + |
| Doxepin (Sinequan) (3) | + | + | ++ | +++ |
| Imipramine (Tofranil) (3) | + | ++ | ++ | + |
| Maprotiline (Ludiomil) (2) | ++ | X | + | ++ |
| Nortryptyline (Pamelor) (2) | ++ | + | + | + |
| Protryptyline (Vivactil) (2) | +++ | + | + | + |
| Trimipramine (Surmontil) (3) | X | X | ++ | ++ |

# Meta-Analysis: TCAs in IBS

- Placebo-controlled trials for FGIDs with TCAs was performed
- These trials include a total 575 patients
- Relative Risk 0.68 (0.56-0.83)
- Meta-analysis demonstrated symptomatic improvement, NNT = 4

[13] AC Ford et al. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. *Gut*. 2009;58:367-378.

# Tricyclic Antidepressants (TCAs)

**Side Effects:**

Anticholinergic

- Constipation
- Dry Mouth
- Blurred Vision
- Urinary Hesitancy
- Esophageal Reflux

Cardiovascular

- Slowed conduction
- Orthostatic hypotension
- Palpitations
- Hypertension

Central Nervous System

- Sedation
- Tremor
- Stimulation
- Myoclonic twitches

Other

- Weight gain
- Sexual dysfunction
- Impotence
- Perspiration

**Dose Range:** 10-200mg

# Selective Serotonin Reuptake Inhibitors (SSRIs)

- Selectively block the reuptake of 5-HT
- Initially increase availability of 5-HT in synaptic cleft
- Eventually reduce sensitivity of somatodendritic and terminal 5-HT1A autoreceptors
- Increase in neurotrophin expression and enhanced transcription of neurotrophic factors, including BDNF

# Meta-Analysis: SSRIs in IBS

- In a 2009 a meta-analysis of 5 randomized, placebo-controlled trials for functional gastrointestinal disorders with SSRIs was performed
- These trials only include a total 230 patients
- Relative Risk 0.62 (0.45-0.87)
- Meta-analysis demonstrated symptomatic improvement, NNT = 4

[13] AC Ford et al. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. *Gut*. 2009;58:367-378.

# Selective Serotonin Reuptake Inhibitors (SSRIs)

Examples: Citalopram (Celexa)
Escitalopram (Lexapro)
Fluoxetine (Prozac)
Fluvoxamine (Luvox)
Paroxetine (Paxil)
Sertraline (Zoloft)

Side Effects: Headache
GI side effects (nausea, diarrhea, heartburn)
Sexual dysfunction (↓libido, delayed orgasm)
Sleep disturbance (insomnia, somnolence)

Dose Range: 10-100mg

# SSRIs and TCAs: Synergy

- Enhance effectiveness of endogenous pain inhibition and modulate hyperalgesia
- Both SSRIs and TCAs may be equally effective in improving IBS symptoms13
- Reported success of combination of SSRIs with TCAs for pain modulation if one alone is insufficient13,14

[13] AC Ford et al. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. *Gut*. 2009;58:367-378; [14] Drossman D. A. et al. Severe and refractory chronic abdominal pain: treatment strategies. *Clin Gastroenterol. Hepatol.* 2008; 6:978-982; [15] Drossman DA. Beyond Tricyclics: new ideas for treating patients with painful and refractory functional gastrointestinal symptoms. Am. *J. Gastroenterol*. 2009; 6:978-982.

# Choosing an Antidepressant (ACG)

- TCAs and SSRIs are more effective than placebo at relieving global IBS symptoms, and appear to reduce abdominal pain
- There is good data on the safety and tolerability of these agents in patients with IBS
- Diarrhea – TCA
- Constipation – SSRI

# Mirtazapine

**Mechanism of Action**

- α2-adrenergic receptor antagonist
- 5-HT2, 5HT3 receptor antagonist
- Potent H1 receptor antagonist

**Side Effects**

- Dry Mouth
- Somnolence
- Sedation
- Weight Gain

# Psychological Treatments

"Collaborative treatment of psychological symptoms with gastroenterology and psychologists has demonstrated improvements in medical symptoms and global self assessment"

[16] Gerson CD, Gerson MD, et al. A Collaborative Health Care Model for the Treatment of Irritable Bowel Syndrome. *Clinical Gastroenterology and Hepatology*. 2003;1:446-452 .

# Psychological Treatment

- **Cognitive Behavioral Therapy** – (CBT) seven studies done comparing CBT to “control” or usual treatment. Total patients = 493
- IBS symptoms persisted in 118 of 279 assigned to CBT or 42.3%. IBS symptoms persisted in 130 of 212 of those assigned to usual care or 61.3%
- NNT = 3

[13] AC Ford et al. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. *Gut*. 2009;58:367-378.

# Benefits of Collaboration

- Increased time with a team of physicians
- Thorough assessment of psychosocial factors
- Expanded treatment plan to include psychotropics commonly used in IBS that are dosed based on patient-specific factors as well as psychotherapy
- Potential to decrease visits to GI clinic and emergency services

# Let's Take It on Home

- The symptoms overlap between IBD and IBS complicates diagnosis and subsequent management of patients with post-IBD IBS
- Assays for inflammation such as calprotectin in feces, allows identification of active IBD and prompts appropriate therapy.
- Therapies directed toward food-derived immune response in patients with post-IBD IBS along with neuromodulation can be effective to manage symptoms and improve quality of life
- A comprehensive approach that embraces lifestyle changes, dietary interventions, medications, and/or behavioral strategies offers the greatest likelihood of sustained treatment benefit for the Disorders of Brain Gut Interactions