

IRRITABLE BOWEL SYNDROME



CHARLENE LEPANE DO MSPH FACG FACOI

ADVANCED ENDOSCOPY/GASTROENTEROLOGIST

ORLANDO VAMC

ASST PROFESSOR OF CLINICAL MEDICINE NSU-COM, LECOM, KCUMB
AND THE UNIVERSITY OF CENTRAL FLORIDA SCHOOL OF MEDICINE

****NO DISCLOSURES****

IBS: LECTURE DETAILS

- Clinical manifestations
- Diagnostic criteria
- Diagnostic approach
- Pathophysiology
 - Brain-gut axis
 - GI motility
 - Visceral hypersensitivity
 - Intestinal inflammation
 - Post infection
 - Alteration in fecal microflora
 - Bacterial overgrowth
 - Food sensitivity
 - Genetics
 - Psychosocial dysfunction
- Treatment
 - Dietary
 - FODMAPS
 - Lactose avoidance
 - Gluten free
 - Fiber
 - Physical activity
 - Adjunctive pharmacologic therapy
 - IBS-C
 - IBS-D
 - Abdominal pain and bloating
 - Refractory symptoms

IRRITABLE BOWEL SYNDROME

- Syndrome-a group of symptoms that consistently occur together, or a condition characterized by a set of associated symptoms
- Irritable bowel syndrome (IBS) is a gastrointestinal syndrome characterized by chronic abdominal pain and altered bowel habits in the absence of any organic cause
- Most commonly diagnosed gastrointestinal (GI) condition
- The prevalence of IBS in North America approximately 10 to 15% (1)
- A population-based study in Europe found an overall prevalence of 11.5% (2)

IRRITABLE BOWEL SYNDROME

- Estimated overall 2:1 female predominance (3)
- Only 15% actually seek medical attention (1)
- Comprises 25 to 50 percent of all referrals to gastroenterologists (4)
- Accounts for a significant number of visits to primary care physicians
- Second highest cause of work absenteeism after common cold
- IBS has been associated with increased health care costs, with some studies suggesting annual costs of up to \$30 billion annually (5) (*Gastro 2002*)

IBS CLINICAL MANIFESTATIONS

- Extraintestinal symptoms
 - Impaired sexual function, dysmenorrhea, dyspareunia, increased urinary frequency and fibromyalgia symptoms (6)
- Chronic abdominal pain
 - Crampy with variable intensity and periodic exacerbations
 - Severity ranges from mild annoying to debilitating
 - Typically exacerbated by emotional stress and eating
 - Defecation often provides some relief
 - Pain NOT compatible with IBS
 - Pain associated with anorexia, malnutrition or weight loss
 - Pain that is progressive or nocturnal

IBS CLINICAL MANIFESTATIONS

- Altered bowel habits
 - Diarrhea
 - Occurs while awake, common in morning or after meals
 - Preceded by lower abdominal cramps and urgency
 - 1/3 of patients with IBS have mucus discharge with stool (7)
 - Blood in stool, nocturnal diarrhea and greasy stool NOT seen with IBS
 - Constipation
 - Lasts for days to months, with episodes of diarrhea or normal bowel function
 - Hard stool, straining and sense of incomplete evacuation

IBS DIAGNOSTIC CRITERIA

- There has been conflicting data regarding the predictive ability of the Manning criteria (1978)
- Rome Criteria
 - In effort to standardize clinical research protocols, an international team published a consensus definition in 1992 called Rome Criteria
 - Revised 2016 now Rome IV Criteria (8) defined as recurrent abdominal pain at least one day per week in the last three months associated with two or more of the following criteria:
 - Related to defecation
 - Associated with a change in stool frequency
 - Associated with a change in stool form (appearance)

IBS DIAGNOSTIC CRITERIA

- Subtypes of IBS based on patient's predominant bowel habit on days with abnormal bowel movements (must be established off motility meds)
- Bristol Stool Form Scale (BSFS) should be used to record stool consistency
- IBS subtypes are defined for clinical practice as follows:
 - IBS-C: usually constipation (type 1 and 2 in the BSFS)
 - IBS-D: usually diarrhea (type 6 and 7 in the BSFS)
 - Mixed IBS: both constipation and diarrhea
 - Unclassified IBS: Patients who meet diagnostic criteria for IBS but cannot be accurately categorized into one of the other three subtypes

DIAGNOSTIC APPROACH IBS

- Diarrhea-predominant IBS
 - Little role for stool cultures with chronic diarrhea except if suspect exposure to *Giardia*
 - Screening for celiac disease with serum IgA antibody to tissue transglutaminase is recommended in IBS-D patients (9) (*Am J Gastro* 2009)
 - 24 hr stool collection can differentiate osmotic vs secretory diarrhea vs malabsorption
 - Many causes of chronic diarrhea such as microscopic colitis require endoscopic evaluation

DIAGNOSTIC APPROACH IBS

- IBS-C
 - Screening tests should be based upon the patient's clinical history
 - A plain film of the abdomen can detect retained stool
 - Sigmoidoscopy or colonoscopy should be performed if structural lesion is suspected
 - Colonoscopy recommended in patients older than 50 because of the increased risk of colon cancer

PATHOPHYSIOLOGY OF IBS

- History of psychosocial factors (anxiety, depression, phobias and daily stressful events)
- Increased visceral hypersensitivity to distention
- Altered GI motility
- Increased levels of pro-inflammatory cytokines
- Increased gut permeability
- Dysregulation of the interaction between the gut and central nervous system
- Altered gut microflora (infection may affect gut permeability & the enteric nervous system)
- Also being considered is the role of food sensitivity and genetic predisposition

PATHOPHYSIOLOGY OF IBS-BRAIN-GUT AXIS

- The Brain-Gut-Axis plays an important role in regulating the behavior of the GI tract
- Central Nervous System (CNS)
- Autonomic nervous system
 - Efferent & afferent nerve fibers to smooth muscle & glands
- Enteric Nervous System
 - Utilizes over 30 neurotransmitters including acetylcholine, dopamine & serotonin (5HT)
 - Communicates with the CNS through parasympathetic & sympathetic nerves
- Gut Wall
 - Layers of smooth muscle, glands, epithelium

PATHOPHYSIOLOGY OF IBS-BRAIN-GUT AXIS

- Signals from the GI tract → brain → modulates changes in motility & secretion
- This axis is an important bidirectional communication system for regulating food intake, digestion, gut sensations, and bowel movements
- Disruptions of this axis can result in IBS
- A study confirmed visceral hypersensitivity via cerebral cortical responses demonstrated on MRI and PET by using balloon distension in the descending colon of IBS patients compared to controls (11) (*Gastroenterology* 1987)

PATHOPHYSIOLOGY OF IBS-BRAIN-GUT AXIS

- Serotonin (5-HT) is a monoamine neurotransmitter which plays an important role in GI motility and mood
- 90% in GI tract (also found on platelets, CNS)
- 5-HT₃ receptors are found on enteric afferent nerves
 - When stimulated by 5-HT (released by enterochromaffin cells in response to distension of the GI wall) → produce cortical responses resulting in nausea, vomiting and abdominal pain
- A 12 year prospective study published in 2012 concluded that disturbances in the gut-brain pathway are dominant in IBS (69) (Gut)

PATHOPHYSIOLOGY OF IBS-GASTROINTESTINAL MOTILITY

- No predominant pattern of motor activity has emerged as a marker for IBS
- Abnormalities observed include
 - Increased frequency and irregularity of luminal contractions
 - Exaggerated motor response to cholecystokinin and meal ingestion in IBS-D (10)
 - Prolonged transit time in IBS-C
- Pharmacologic stimulation of gut motility in IBS-C patients has been reported to reduce gas retention and improve symptoms, reinforcing motility is a factor in IBS (*Dig Dis Sci* 2010)

PATHOPHYSIOLOGY OF IBS-VISCERAL HYPERSENSITIVITY

- Visceral hypersensitivity is common with IBS
- Perception results from stimulation of receptors in the gut wall → signals via afferent neural pathways → dorsal horn of the spinal cord → brain
- Studies demonstrate pain caused by balloon distention in intestines was experienced at lower balloon volumes in IBS compared to controls, thus suggesting receptor hypersensitivity (12) (*Am J Gas* 2006)
- 50% of IBS patients have increased abdominal girth associated with bloating(13)

PATHOPHYSIOLOGY OF IBS-VISCERAL HYPERSENSITIVITY

- IBS pts do not have increased volume of gas, however, exhibit impaired transit of intestinal gas loads which results in bloating(14,15)
- It is unclear if hypersensitivity is mediated by local GI nervous system, by central modulation from the brain, or by combination of these two
- GI mediators (serotonin, kinins) or increases in spinal cord excitability (d/t activation of an N-methyl-D-aspartate (NMDA) receptor) may contribute to visceral hypersensitivity, however, further study is necessary (16) (*Gastro 2004*)

PATHOPHYSIOLOGY OF IBS-INTESTINAL INFLAMMATION

- Alterations in immune cells and markers are seen in IBS-D (17)
- Increased lymphocytes reported in colon and small intestine in IBS
 - A study with full-thickness jejunal biopsies obtained in 10 patients with severe IBS found increase in lymphocyte infiltration in the myenteric plexus in nine patients and neuron degeneration in six patients (18) (*Gastro 2002*)
 - Lymphocytes release mediators (nitric oxide, histamine and proteases) leading to abnormal motor and visceral responses within the intestine
- Stool examinations from IBS-D patients have revealed a high level of serine-protease activity
 - In one study, serine-protease increased colonic cellular permeability and visceral pain in mice, suggesting intestinal inflammation (19) (*Gut 2008*)

PATHOPHYSIOLOGY OF IBS-INTESTINAL INFLAMMATION

- Mast cells are effector cells of the immune system
 - Increased in the terminal ileum, jejunum, and colon of IBS patients (20)
 - A study published in *Gastroenterology* 2004 demonstrated a correlation between abdominal pain in IBS and the presence of activated mast cells in proximity to colonic nerves (21)
- Cytokines are proteins that are mediators of immune responses
 - Elevated levels of plasma pro-inflammatory interleukins have been observed in patients with IBS (22)
 - In addition, mononuclear cells of IBS patients produce higher amounts of tumor necrosis factor than healthy controls(22), thus suggesting inflammation indeed plays a role in IBS

PATHOPHYSIOLOGY OF IBS-POST INFECTIOUS

- Post-infectious IBS is associated with bacterial, protozoan, helminth and viral infections (23)
- Two meta-analyses demonstrated an increased risk of IBS in patients with acute gastroenteritis (24) (*Am J Gastro* 2006)
 - The larger review of 18 studies (10 controlled studies) reported the pooled incidence of IBS was 10%, and odds of developing IBS are increased six-fold after an acute GI infection (25)
 - Risk factors for postinfectious IBS included young age, prolonged fever, longer duration of initial infection, anxiety, and depression

PATHOPHYSIOLOGY OF IBS-ALTERATION IN FECAL MICROFLORA

- There is speculation that changes in composition of fecal flora are associated with IBS
- Fecal microbiota in individuals with IBS differ from healthy controls (31)
 - Supported by a study that demonstrated that colonic hypersensitivity in IBS patients can be transferred to germ-free animals by inoculating the animals with fecal microbiota from IBS patients (32) (*Neurogastr Mot* 2013)
 - Colonic hypersensitivity was not seen in the transfer of fecal bacteria of controls to the same germ-free animals

PATHOPHYSIOLOGY OF IBS-ALTERATION IN FECAL MICROFLORA

- Considering potential microflora alterations in IBS, it is thought that patients with IBS-D would benefit from probiotics (which influence the composition and metabolism of the microflora)
- A randomized trial found that administration of *L. plantarum* did not significantly affect the intestinal flora of patients with IBS, however, patients who received the probiotic had a decrease in symptoms of flatulence (33) (*Am J Gastro* 2000)

PATHOPHYSIOLOGY OF IBS-BACTERIAL OVERGROWTH

- SIBO is an increased number and/or type of bacteria in the upper GI tract
- A postulated relationship between SIBO and IBS
- Studies demonstrate abnormal breath hydrogen levels in IBS patients after receiving a test dose of a carbohydrate, as well as improvement in symptoms after eradication of the overgrowth (34,35)
- Increased methane production (a gas byproduct of intestinal bacteria) has been associated with IBS-C, implicating bacteria in the pathophysiology (36)
(*Am J Gastro* 2007)

PATHOPHYSIOLOGY OF IBS-FOOD SENSITIVITY

- The role of food in the pathophysiology of IBS is not clear
- Food specific antibodies
 - Data reporting intolerance to specific foods by skin prick testing have been conflicting
 - The number of positive food skin-prick tests was greater in IBS patients compared with controls in one study, however in another study, challenge with those foods that caused positive skin prick tests did not exacerbate symptoms (37,38)
- Carbohydrate malabsorption
 - Fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs) enter the distal small bowel and colon where they are fermented, leading to symptoms and increased intestinal permeability and gas formation (39)

PATHOPHYSIOLOGY OF IBS-FOOD SENSITIVITY

- Fructose intolerance has been suggested as a possible form of carbohydrate malabsorption contributing to GI symptoms
- One small controlled trial found that dietary restriction of fructose improved symptoms in patients with IBS (40) (*Clin Gastro and Hep* 2008)
- Gluten sensitivity
 - A study suggested that in patients without villous atrophy, but + IgG antigliadin and expression of HLA-DQ2 may predict response to a gluten free diet in patients with IBS-D (41) (*Clin Gastro and Hep* 2008)
 - Another study looked at IBS-D patients without celiac disease
 - Ingestion of gluten altered small intestinal permeability and increased frequency of bm in patients who were HLA-DQ2/8 + compared with those who were HLA-DQ2/8 - (42) (*Gastro* 2013)

PATHOPHYSIOLOGY OF IBS-GENETICS

- Familial studies suggest a modest contribution of genetics to the development of IBS
- Although one study demonstrated concordance rates for IBS in monozygotic twins ranged from 2 to 22% and dizygotic twins ranged from 1 to 9% (43), other studies demonstrate no difference in concordance rates
- Another study suggested having a parent with IBS was a greater independent predictor of IBS than having an affected twin
 - This suggests IBS could be due to social learning in addition to genetics (44) (*Gastro 2001*)

PATHOPHYSIOLOGY OF IBS-GENETICS

- Genotyping studies have shown an association between IBS and polymorphisms in the serotonin transporter gene
 - Modified serotonin reuptake alters intestinal peristalsis (45) (*Gut* 2004)
- Data suggests IBS patients may be genetically predisposed to an altered pattern of anti-inflammatory cytokine interleukin production
 - Further supports role of inflammation and genetics with the disorder (46) (*Gut* 2003)

PATHOPHYSIOLOGY OF IBS-PSYCHOSOCIAL DYSFUNCTION

- In one study IBS patients reported more lifetime and daily stressful events than control groups (47) (*Am J Gastro* 2004)
- Long term data has also demonstrated patients with IBS exhibit increased anxiety, depression, phobias, and somatization (48)
- One unifying hypothesis concerning the role of stress and psycho neuroticism in IBS is based upon corticotropin releasing factor (CRF)
 - CRF is a peptide released from the paraventricular nucleus and considered to be a major mediator of the stress response
 - Data suggests that over-activity in the brain CRF-receptor signaling system contributes to anxiety disorders and depression (49)
 - A study reports IV administration of CRF increased abdominal pain and colonic motility in IBS patients to a higher degree than normal controls (50) (*Gut* 1998)

TREATMENT-DIETARY MODIFICATIONS- FODMAPS

- Patients may benefit from:
 - Exclusion of gas-producing foods
 - A diet low in fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs)
 - Lactose and gluten avoidance
- In a randomized trial individuals with documented IBS were assigned to a low FODMAP diet vs traditional IBS diet (avoidance of large meals; reduced intake of fat, insoluble fibers, caffeine, and gas-producing foods such as beans, cabbage, and onions) for 4 weeks (51) (*Gastro 2015*)
 - A significant reduction in IBS symptom severity were actually documented in both dietary groups
- Therefore, patients with IBS should be advised to exclude foods that increase flatulence (beans, onions, celery, carrots, raisins, bananas, apricots, prunes, Brussels sprouts, wheat germ, pretzels, and bagels) and adhere to low FODMAPS diet

TREATMENT-DIETARY MODIFICATIONS- LACTOSE AVOIDANCE

- Trial of a lactose-free diet should be considered in patients who complain of persistent abdominal bloating despite exclusion of gas-producing foods
- Individuals who have no evidence of lactose intolerance on breath test but who have symptoms with ingestion of milk may have intolerance to other milk components (ex. cow milk protein)
 - They may tolerate milk from other mammals or other milks (soy, cashew, almond)
- The incidence of lactose malabsorption is not higher in patients with IBS
- However, patients with IBS and lactose intolerance have an exaggerated symptom response to lactose ingestion (52) (*Am J Gastro* 2013)

TREATMENT-DIETARY MODIFICATIONS- GLUTEN FREE

- A two-week trial of a gluten-free diet suggested in IBS-D patients with significant abdominal bloating/flatulence whose symptoms have failed to improve with a low FODMAP diet and avoidance of gas-producing foods
- Gluten has been demonstrated to alter bowel barrier functions in patients with IBS-D
 - Higher SB permeability by increasing expression of zona occludens
 - It does not alter transit or histology
 - It does not alter colonic permeability

TREATMENT-DIETARY MODIFICATIONS- GLUTEN FREE

- In a randomized trial, 34 patients with no evidence of celiac disease (HLA-DQ2/DQ8 negative, or normal duodenal biopsies) were assigned to a diet with gluten vs gluten free for 6 weeks (53) (*BMJ* 2012)
 - Patients documented more symptoms on a gluten-containing diet (68 versus 40%)
- Further studies warranted

TREATMENT-DIETARY MODIFICATIONS-FIBER

- Role of fiber in patients with IBS is controversial, but given the absence of serious side effects and potential benefit, it should be considered in IBS-C
- A starting dose of psyllium is 1/2 to 1 Tbsp daily
- A meta-analysis of pooled data from 6 trials used a combined endpoint for abdominal pain and global IBS symptoms and demonstrated improvement in symptoms with psyllium vs placebo (53) (*BMJ* 2012)

TREATMENT-PHYSICAL ACTIVITY

- Physical activity should be encouraged in all patients, but especially in IBS
- In a randomized trial, 102 patients with IBS were assigned to increased physical activity vs maintenance of current activity levels (54) (*Am J Gastro* 2014)
 - Increased physical activity composed 20 to 60 minutes of moderate to vigorous activity 3-5 days per week
 - 75% patients completed the study (38 in the physical activity arm and 37 in the control arm)
 - After 12 weeks, increased physical activity arm showed clinical improvement in the severity of IBS symptoms compared to control group (43 versus 26 percent, $p = 0.07$)
 - They were also less likely to have worsening of their IBS symptoms compared to controls (8 versus 23 percent)

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: IBS-CONSTIPATION

- In patients with IBS-C who have failed fiber benefit, polyethylene glycol (PEG) is suggested
- PEG is inexpensive, widely available, and has fewer side effects compared to other osmotic laxatives (lactulose, MOM)
 - 17 g of powder dissolved in 8 ounces of water daily
 - Side effects are bloating and abdominal discomfort
- Treatment with PEG improves constipation but not abdominal pain
 - A randomized trial demonstrated patients treated with PEG had significantly more spontaneous bowel movements, improvement in stool consistency, and reduction in the severity of straining
 - There was no significant difference in the severity of bloating or abdominal pain (55) (*Am J Gastro* 2013)

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: IBS-CONSTIPATION

- Lubiprostone (Amitiza) is a locally acting chloride channel activator that enhances chloride-rich intestinal fluid secretion and motility
 - Approved for treatment of IBS-C in women 18 years and older
 - Dose for IBS-C (8 micrograms BID) is lower than the approved dose for CIC and opioid induced constipation (24 ug BID)
 - Has not been directly compared with other treatment options for IBS-C
 - Long-term safety remains to be established

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: IBS-CONSTIPATION

- Efficacy has been demonstrated in two randomized trials in which the majority of patients were women
- 1154 adults (92 percent women) with IBS-C were randomly assigned to Amitiza (8 micrograms twice daily) vs placebo for 12 weeks
- Patients randomized to lubiprostone were significantly more likely to achieve an overall response of improvement of constipation (18 versus 10%)
- Most common ADR was nausea (8 versus 4 percent)
- A follow-up open-label study that included 522 patients demonstrated that benefits of lubiprostone persisted or increased at 52 weeks, thus confirming it's long term efficacy (56)

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: IBS-CONSTIPATION

- Linacotide (Linzess) is a guanylate cyclase agonist that stimulates intestinal fluid secretion and transit
- Approved for treatment of IBS-C at a dose of 290 micrograms daily (CIC 145 ug daily)
- The efficacy in the treatment of IBS-C has been demonstrated in two randomized controlled trials
- In one trial, 800 patients with IBS-C were assigned to linacotide or placebo for 12 weeks
 - After 12 weeks a decrease of abdominal pain and increase of bm was significantly greater with linacotide compared to placebo (34 versus 21%)

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: IBS-CONSTIPATION

- Linaclootide also demonstrated a significant improvement in secondary endpoints:
 - Abdominal pain/discomfort
 - Bloating
 - Straining
 - Stool consistency
 - Number of bowel movements per week compared to placebo
- Diarrhea was the most common side effect, causing discontinuation of treatment in 5.7% of patients treated with linaclootide vs 0.3% in patients receiving placebo

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: IBS-CONSTIPATION

- A second randomized trial assessed the efficacy of long-term use of linaclotide (58)
 - In this trial, 804 patients with IBS-C were randomly assigned to receive linaclotide (266 micrograms daily) or placebo for 26 weeks
 - Patients randomized to linaclotide demonstrated a significant improvement in the same composite primary endpoint as compared with placebo (38 vs 14%)
- Long-term risks (>26 wks) of linaclotide are unknown

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: IBS-DIARRHEA

- Initial treatment of IBS-D is loperamide 2 mg 45 minutes before a meal on regularly scheduled doses
- Loperamide is an opioid agonist that does not cross the blood-brain barrier and has no analgesic properties or potential for addiction
- In gut inhibits the release of acetylcholine and prostaglandins
 - Reduces peristalsis
- Should be used in limited doses, on an as-needed basis (maximum daily dose 16 mg/day)
- Three trials suggested that loperamide was more effective than placebo for treatment of diarrhea by decreasing stool frequency and consistency, but not for the symptoms of bloating, abdominal discomfort, or global IBS symptoms (59) (*Scand J Med* 1987)

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: IBS-DIARRHEA

- Eluxadoline (Viberzi) works by activating receptors in the CNS to lessen bowel contractions in IBS-D
 - Mu opioid receptor agonist
 - Deta receptor antagonist
 - Kappa receptor agonist

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: IBS-DIARRHEA

- In 2 studies, 2427 adults with IBS-D were randomly assigned to eluxadoline at a dose of 75 mg, 100 mg, or placebo twice daily for 26 and 52 weeks, respectively (60)
 - Primary endpoint was decrease in abdominal pain and improvement in stool consistency on the same day, for at least 50% of the days from weeks 1 through 12 and from weeks 1 through 26
 - A significantly higher proportion of patients receiving eluxadoline (100 mg twice daily) achieved the primary endpoint compared to placebo in both trials (29 versus 19%; 33 versus 20%)
 - ADR's were nausea, constipation, and abdominal pain
 - Contraindicated in history of obstruction, IBS-C, SOD, ETOH, previous pancreatitis

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: IBS-DIARRHEA

- Bile acid sequestrants (ie cholestyramine, colestipol) can be considered
- ADR's are bloating, flatulence, abdominal discomfort, and constipation
- 50% patients with functional diarrhea and IBS-D have bile acid malabsorption (61)
 - Bile acids cause diarrhea by stimulating colonic secretion and motility
- In a randomized trial in which 24 patients with IBS-D were assigned to treatment with colesevelam (Welcol) (1.875 g twice daily) vs placebo
 - Welcol decreased colonic transit time with an average delay of four hours as compared with placebo (62)
(*Arc Clin Gastr Hep* 2010)

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: IBS-DIARRHEA

- Alosetron (Lotronex) 5HT-3 antagonist
 - Approved for the treatment of severe IBS-D in female patients with at least 6 mo of symptoms and who have failed to respond to all other conventional treatment
 - Modulates visceral afferent activity from GI tract, thereby decreasing colonic motility and secretion, and may improve abdominal pain
- In a meta-analysis that included 14 randomized trials, treatment with 5HT-3 antagonists resulted in a global improvement in IBS symptoms and relief of abdominal pain and discomfort (63) (*Clin Gastro and Hep* 2008)

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: IBS-DIARRHEA

- Side effects of ischemic colitis and complications of severe constipation led to the withdrawal from the market in US in 2000
- After evaluation of post-marketing data, its again available in US under criteria:
 - Lower starting dose (0.5 mg BID x 4 wk max 2 mg/day)
 - By physicians enrolled in the alosetron prescribing program
 - Approved for female patients exclusively

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: ABDOMINAL PAIN AND BLOATING

- Antispasmodics
 - Those that directly affect intestinal smooth muscle relaxation (ie Colofac (mebeverine)); antispasmodic with no anticholinergic property
 - Those that act via their anticholinergic or antimuscarinic properties (ie Bentyl (dicyclomine) and hyoscyamine)
- The selective inhibition of GI smooth muscle by antispasmodics and peppermint oil reduce stimulated colonic motor activity

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: ABDOMINAL PAIN AND BLOATING

- In a 2011 meta-analysis, antispasmodics were associated with a significant improvement in abdominal pain, global assessment and symptom score as compared with placebo (64) (Cochrane database review 2011)
- Suggested doses include:
 - Dicyclomine 20 mg orally four times daily as needed
 - Hyoscyamine 0.125 to 0.25 mg orally or sublingually three to four times daily as needed
 - Sustained release hyoscyamine 0.375 to 0.75 mg orally every 12 hours

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: ABDOMINAL PAIN AND BLOATING

- Antidepressants have analgesic properties independent of their mood improving effects
- Tricyclic antidepressants (TCAs) via their anticholinergic properties slow intestinal transit time for IBS-D
- TCAs should be used cautiously in patients with constipation
- Antidepressants should be started at low doses
- There is a delayed onset of action of antidepressants, therefore three to four weeks of therapy should be attempted before increasing the dose
- Amitriptyline, nortriptyline, and imipramine can be started at a dose of 10 to 25 mg at bedtime (ADR drowsiness)
- If the patient is intolerant of one TCA, another may be tried (Imipramine less ADR)

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: ABDOMINAL PAIN AND BLOATING

- Compared to TCA's, there is less published experience with other antidepressants such as selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)
- Results of the few published trials (mainly with SSRIs) have been inconsistent
- A 2015 meta-analysis that included 12 randomized trials of antidepressants and TCA's in adults with IBS concluded that antidepressants and TCA's were significantly more effective as compared with placebo in improving global IBS symptoms (RR 1.38, 95% CI 1.08-1.77) (65)

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: SUMMARY OF MEDICATIONS

- TCA (tricyclic antidepressants) (desipramine, amitriptyline [Elavil] and nortriptyline)
 - NE > serotonin receptor uptake inhibition
 - Effective in treatment of chronic D, pain and depression
- SNRI (serotonin norepinephrine reuptake inhibitor) (duloxetine [Cymbalta], venlafaxine [Effexor], desvenlafaxine [Pristiq])
 - NE and serotonin receptor uptake inhibitions
 - Effective with pain, anxiety and depression
- SSRI (selective serotonin reuptake inhibitors) (fluoxetine [Prozac], paroxetine [Paxil], citalopram [Celexa])
 - Serotonin reuptake inhibition
 - Effective with constipation, anxiety and depression

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: ABDOMINAL PAIN AND BLOATING

- Antibiotics should be considered in moderate to severe IBS without constipation, particularly those with bloating, who have failed to respond to other therapies (ie FODMAPs diet, antispasmodics, and TCAs)
 - A two-week trial of rifaximin (Xifaxan) 550 mg TID is recommended
- In a meta-analysis of five randomized trials, rifaximin was more efficacious than placebo for global IBS symptom improvement (OR 1.57) and was significantly more likely to be associated with decreased bloating vs placebo (OR 1.55) (66)

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: ABDOMINAL PAIN AND BLOATING

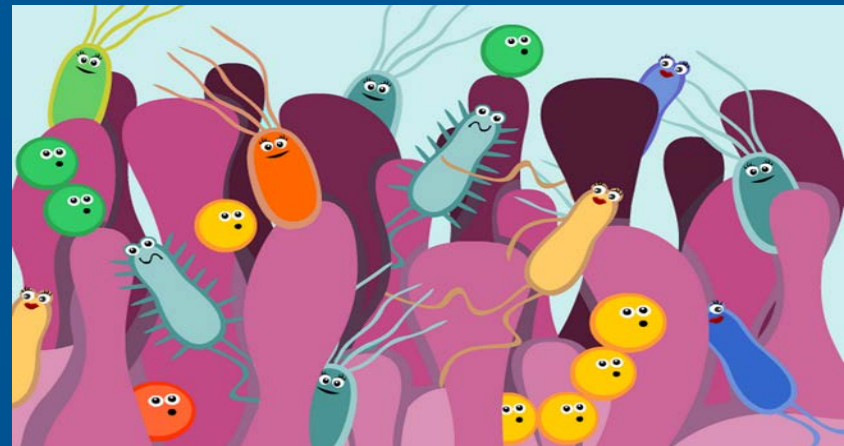
- In the two largest randomized trials (TARGET 1 and TARGET 2) that were included in the meta-analysis, rifaximin-treated patients also experienced an improvement in diarrhea vs placebo
- In these trials, 1260 patients with IBS without constipation were assigned to receive either rifaximin 550 mg three times daily or placebo for 14 days, then followed for 10 weeks (67) (*NEJM 2011*)
- Rifaximin patients had:
 - adequate relief of global IBS symptoms (41 versus 32% placebo)
 - relief of bloating (40 versus 30%)
 - improvement in daily stool consistency (76 versus 66%)

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: ABDOMINAL PAIN AND BLOATING

- Although probiotics have been associated with an improvement in symptoms, the magnitude of benefit and the most effective species and strain are uncertain
- Live probiotic cultures are available in fermented dairy products and probiotic fortified foods
- Tablets, capsules, powders, and sachets containing the bacteria in freeze-dried form are also available
- Few have been sufficiently developed in basic and clinical research to warrant approval for health claim status by FDA (Except VSL3)

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: ABDOMINAL PAIN AND BLOATING

- VSL#3 has the highest concentration of beneficial bacteria available (from 112.5 billion per capsule to 900 billion per packet), with 8 strains of bacteria in specific concentrations that have been chosen to produce optimal intestinal diversity
- VSL#3 was recognized by the American College of Gastroenterology Practice Parameter Committee as an effective tool for the management of pouchitis
- VSL#3 is supported by several double-blind, placebo-controlled studies

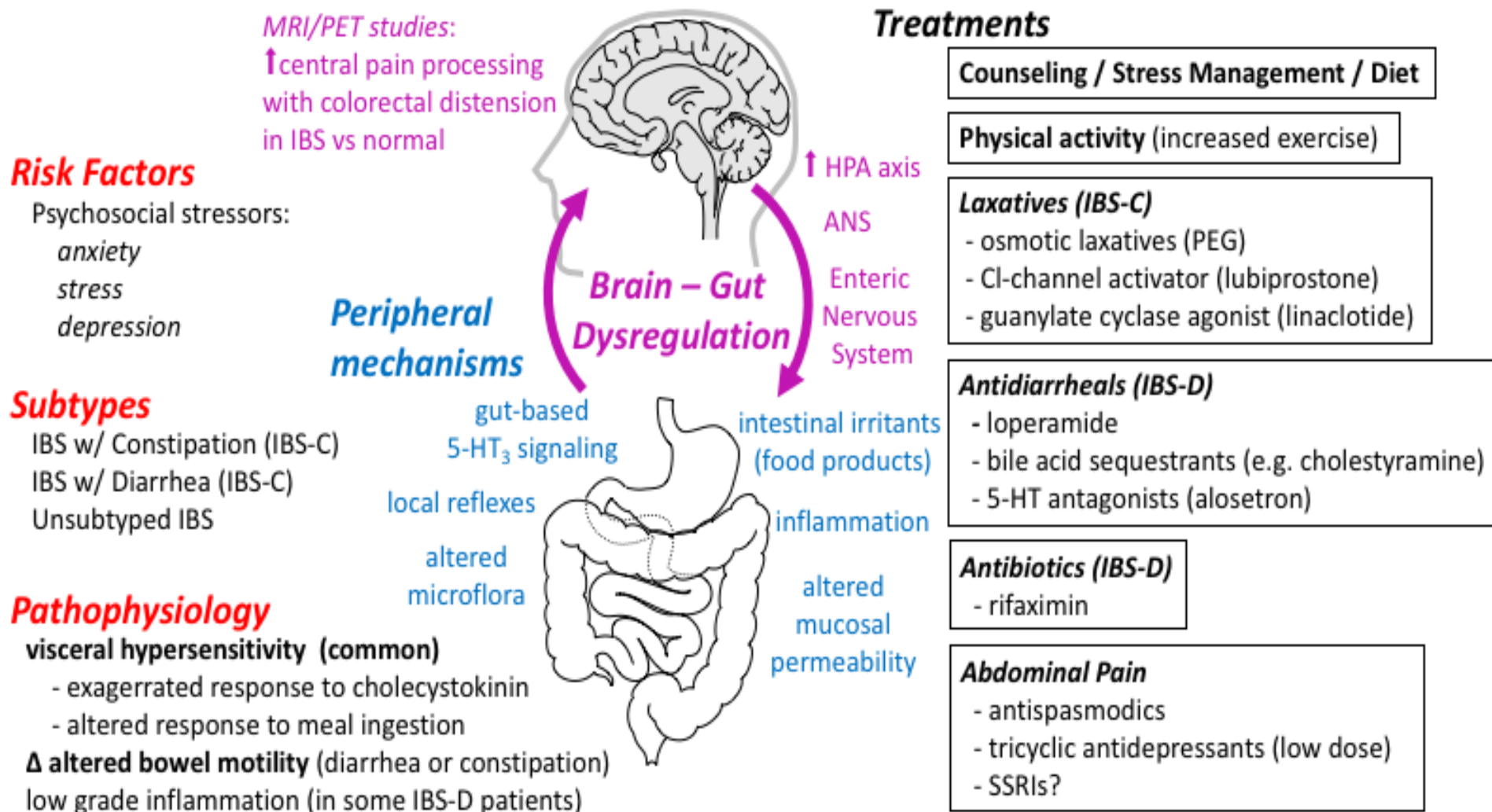


TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: REFRACTORY SYMPTOMS

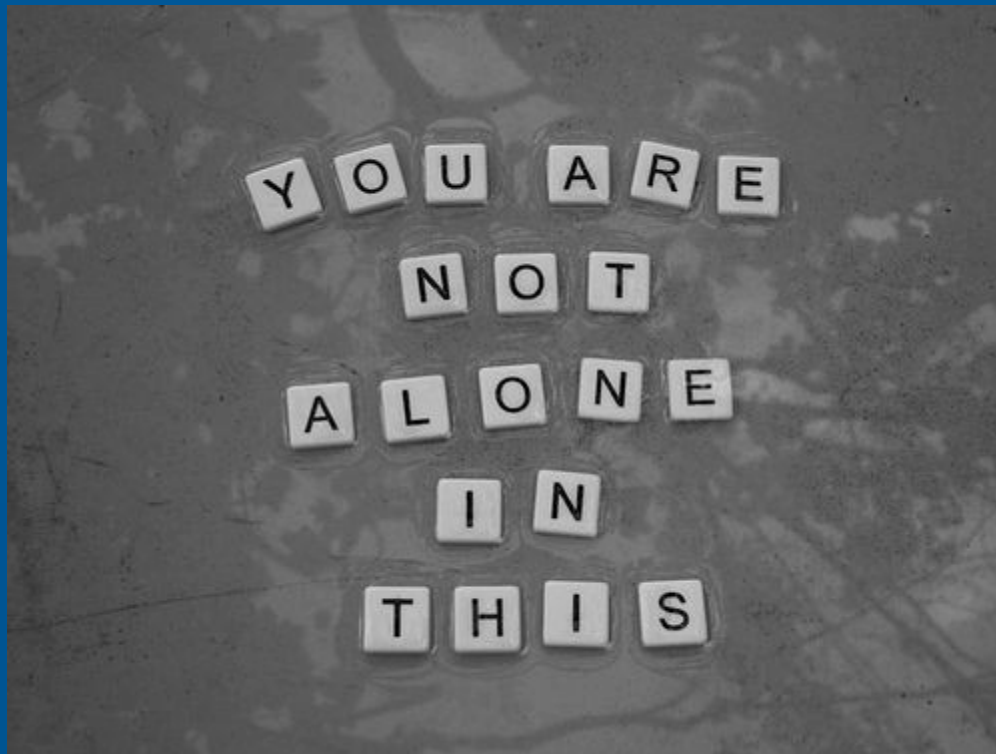
- Patients with continued symptoms despite adjunctive pharmacologic therapy mandate a careful reassessment
 - Compliance, misdiagnosis
- Anxiolytic agents in patients with refractory IBS should be limited to short-term (less than two weeks) reduction of acute situational anxiety that may be contributing to symptoms
 - Side effects of anxiolytics include the risk of habituation, rebound withdrawal, and drug interactions
 - Benzodiazepines may lower pain thresholds by stimulating gamma aminobutyric acid (GABA) receptors, thereby decreasing brain serotonin
- Other therapies have been evaluated in patients with IBS (herbs, acupuncture and enzyme supplementation) but their role in the treatment of IBS remains uncertain
- Ketotifen, a mast cell stabilizer, has been studied for the treatment of IBS based upon the theory that mast cell activation contributes to visceral hypersensitivity (68) (*Gut* 2010)

SUMMARY

Irritable Bowel Syndrome



UNDERSTAND IBS, UNDERSTAND TREATMENT
OPTIONS, AND MOST IMPORTANTLY LET
YOUR PATIENT KNOW THAT THEY ARE NOT
ALONE



THANK YOU



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