IRRITABLE BOWEL SYNDROME

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****NO DISCLOSURES****

IRRITABLE BOWEL SYNDROME

- Irritable bowel syndrome (IBS) is a gastrointestinal syndrome characterized by chronic abdominal pain and altered bowel habits in the absence of any organic cause
- It is the most commonly diagnosed gastrointestinal condition
- The prevalence of IBS in North America estimated from population-based studies is approximately 10 to 15 percent (1)
- A population-based study in Europe found an overall prevalence of 11.5 percent (a value similar to that noted in reports in the United States); however, the prevalence varied widely among countries (2)
- Estimated overall 2:1 female predominance in North America (3)
- Only about 15 percent of those affected 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, and is the second highest cause of work absenteeism after the common cold
- IBS has been associated with increased health care costs, with some studies suggesting annual direct and indirect costs of up to $30 billion (5)

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, malnutrtion or weight loss
    - Pain that is progressive or nocturnal

IBS CLINICAL MANIFESTATIONS

- Altered bowel habits
  - Diarrhea
    - Loose stool of varying volume
    - 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)
    - Diarrhea NOT seen with IBS is blood stool, nocturnal diarrhea or greasy stool
  - 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

- Manning criteria (1978)
- There have been conflicting data regarding the predictive ability of the Manning criteria

Manning criteria for the diagnosis of irritable bowel syndrome*

Pain relieved with defecation
More frequent stools at the onset of pain
Looser stools at the onset of pain
Visible abdominal distention
Passage of mucus
Sensation of incomplete evacuation

* The likelihood of irritable bowel syndrome is proportional to the number of Manning criteria that are present.

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IBS DIAGNOSTIC CRITERIA

- Rome criteria
  - In effort to standardize clincal research protocols, an international team published a consesus definition in 1992 called the Rome criteria
  - Revised 2016 now Rome IV criteria (8) defined as recurrent abdominal pain, on average, at least one day per week in the last three months asociated 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 are recognized based on the patient's reported predominant bowel habit on days with abnormal bowel movements
- The Bristol Stool Form Scale (BSFS) should be used to record stool consistency
- Subtypes can only confidently be established when the patient is evaluated of medications used to treat bowel habit abnormalities
- IBS subtypes are defined for clinical practice as follows:
  - IBS with predominant constipation: Patient reports that abnormal bowel movements are usually constipation (type 1 and 2 in the BSFS)
  - IBS with diarrhea: Patient reports that abnormal bowel movements are usually diarrhea (type 6 and 7 in the BSFS)
  - Mixed IBS: Patient reports that abnormal bowel movements are usually both constipation and diarrhea (more than one-fourth of all the abnormal bowel movements were constipation and more than one-fourth were diarrhea)
  - Unclassified IBS: Patients who meet diagnostic criteria for IBS but cannot be accurately categorized into one of the other three subtypes.

BRISTOL STOOL CHART

	Type 1	Separate hard lumps	Very constipated
	Type 2	Lumpy and sausage like	Slightly constipated
	Type 3	A sausage shape with cracks in the surface	Normal
	Type 4	Like a smooth, soft sausage or snake	Normal
	Type 5	Soft blobs with clear-cut edges	Lacking fibre
	Type 6	Mushy consistency with ragged edges	Inflammation
	Type 7	Liquid consistency with no solid pieces	Inflammation

DIAGNOSTIC APPROACH IBS

- Patients are identified as having a symptom complex compatible with IBS based upon the Rome IV criteria
- Routine laboratory studies (complete blood count, chemistries) are normal in IBS
- "Alarm" or atypical symptoms which are not compatible with IBS include:
  - Rectal bleeding
  - Nocturnal or progressive abdominal pain
  - Weight loss
  - Laboratory abnormalities such as anemia, elevated inflammatory markers, or electrolyte disturbances
  - Patients with one of these alarm symptoms require further imaging studies and/or colonoscopy

DIAGNOSTIC APPROACH IBS

- In patients who have symptoms suggestive of IBS, no alarm symptoms and no family history of inflammatory bowel disease or colorectal cancer, a limited number of diagnostic studies can rule out organic illness in over 95 percent of patients
- Diarrhea-predominant IBS
  - There is little role for stool cultures in patients with chronic diarrhea except for patients with possible exposure to Giardia
  - Screening for celiac disease with serum IgA antibody to tissue transglutaminase is recommended in patients with diarrhea-predominant IBS (9)

MANY CAUSES OF CHRONIC DIARRHEA SUCH AS MICROSCOPIC COLITIS REQUIRE ENDOSCOPIC EVALUATION

- A twenty-four hour stool collection should be considered to differentiate osmotic vs secretory diarrhea vs malabsorption
- Many causes of chronic diarrhea such as microscopic colitis require endoscopic evaluation

- In patients with constipation as the predominant symptom, screening tests should 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

- The traditional focus has been on alterations in gastrointestinal motility and on visceral hypersensitivity
- More recent studies have considered the role of inflammation, alterations in fecal flora, and bacterial overgrowth
- Also being considered is the role of food sensitivity and genetic predisposition

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, prolonged transit time in constipation-predominant IBS, and an exaggerated motor response to cholecystokinin and meal ingestion in diarrhea-predominant IBS (10)
- The relevance of these motor function alterations to symptoms has yet to be established
- However, pharmacologic stimulation of gut motility in IBS patients has been reported to reduce gas retention and improve symptoms, suggesting that a motility disturbance underlies this complaint in some patients

PATHOPHYSIOLOGY OF IBS-VISCERAL HYPERSENSITIVITY

- **Visceral hypersensitivity** (increased sensation in response to stimuli) is a frequent finding
- Perception in the gastrointestinal (GI) tract results from stimulation of various receptors in the gut wall, which signals via afferent neural pathways to the dorsal horn of the spinal cord and ultimately to the brain
- Several studies have focused on selective hypersensitization of visceral afferent nerves in the gut, triggered by bowel distention or bloating, as a possible explanation for IBS symptoms
- Studies have shown that in patients with IBS, awareness and pain caused by balloon **distention** in the intestine are experienced at lower balloon volumes compared with controls, suggesting receptor hypersensitivity (11)
    - This possible increase in sensitivity may be specific for visceral afferents, since it is reported that patients with IBS have normal or even increased thresholds to somatic pain (12)

PATHOPHYSIOLOGY OF IBS-VISCERAL HYPERSENSITIVITY

- 50% of patients with IBS (mainly those with constipation) have a measurable increase in abdominal girth associated with **bloating** (sensation of abdominal fullness), although this may not be related to the volume of intestinal gas (13)
- Patients who complain of bloating and excess gas actually had volumes of gas in the GI tract similar to asymptomatic controls, but exhibit impaired transit of intestinal gas loads (14)
- Another study, comparing the effect of a given lipid load on gas motility in patients with IBS and controls, found that IBS patients exhibited a heightened inhibitory response of motility to the introduction of a low lipid load (15)
- It is unclear whether heightened sensitivity of the intestines to normal sensations is mediated by the local GI nervous system, by central modulation from the brain, or by some combination of the two
- Gastrointestinal mediators (serotonin, kinins) or increases in spinal cord excitability due to activation of an N-methyl-D-aspartate (NMDA) receptor may contribute to ventral hypersensitivity (16)

PATHOPHYSIOLOGY OF IBS-INTESTINAL INFLAMMATION

- Immunohistologic investigation demonstrates **mucosal immune system activation** characterized by alterations in particular immune cells and markers in some patiets with diarrhea-predominant IBS and patients with presumed postinfectious IBS (17)
- **Increased lymphocytes** have been reported in the colon and small intestine in patients with IBS
  - One study in which full-thickness jejunal biopsies were obtained in 10 patients with severe IBS found an increase in lymphocyte infiltration in the myenteric plexus in nine patients and neuron degeneration in six patients (18)
- Lymphocytes release mediators (nitric oxide, histamine and proteases) capable of stimulating the enteric nervous system, leading to abnormal motor and visceral responses within the intestine
- Stool examinations from diarrhea-predominant IBS patients have revealed a high level of serine-protease activity (19)
  - A fecal extract from these patients, when infused intra-colonically into mice, increased colonic cellular permeability and visceral pain in the mice; these effects were prevented by serine protease inhibitors
- The role of intestinal serine-proteases in the pathophysiology of IBS remains under investigation

PATHOPHYSIOLOGY OF IBS-INTESTINAL INFLAMMATION

- **Mast cells** are effector cells of the immune system
  - Increased numbers have been demonstrated 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 proinflammatory interleukins have been observed in patients with IBS (22)
  - In addition, peripheral blood mononuclear cells of IBS patients produce higher amounts of tumor necrosis factor than healthy controls(22)

PATHOPHYSIOLOGY OF IBS-POST INFECTIOUS

- The development of irritable bowel syndrome (IBS) following **infectious enteritis** has been suggested clinically based on acute diarrheal illness preceding the onset of irritable bowel symptoms
- The increased risk of postinfectious IBS is associated with bacterial, protozoan, helminth infections, and viral infections (23)
- Two meta-analyses demonstrated an increased risk of IBS in patients who experienced an episode of acute gastroenteritis (24)
  - The larger review of 18 studies (10 controlled studies) reported that the pooled incidence of IBS was ten percent, and the odds of developing IBS are increased sixfold after an acute gastrointestinal (GI) infection (25)
  - Risk factors for postinfectious IBS included young age, prolonged fever, anxiety, and depression
  - A longer duration of the initial infection has also been associated with increased risk for IBS

PATHOPHYSIOLOGY OF IBS-POST INFECTIOUS

- The cause of bowel symptoms following acute infection is uncertain, although several theories have been proposed:
- The development of idiopathic bile acid **malabsorption** has been observed following enteric infections, which may be result in diarrhea-predominant IBS (26)
- An increase in **serotonin-containing enteroendocrine cells and T lymphocytes**, has been demonstrated following acute Campylobacter enteritis (27)
  - The increased serotonin levels lead to increased GI motility and visceral hypersensitivity
  - Neither a reduction in enteroendocrine cells nor improvement in symptoms was observed in a controlled trial of glucocorticoids given to patients with post-infectious IBS (28)
  - One study suggested that increased numbers of enteroendocrine cells and depression were independent predictors of developing post-infectious IBS (29)
- The use of **antibiotics** for GI or other infections was observed to be a risk factor for developing functional bowel symptoms (30)

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 and vary with the predominant symptom (31)
- This is 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 but not from healthy controls (32)
- Considering potential microflora alterations in IBS, it is thought that patients with diarrhea-predominant IBS 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)

PATHOPHYSIOLOGY OF IBS-BACTERIAL OVERGROWTH

- Small intestinal bacterial overgrowth (SIBO) is associated with an increased number and/or type of bacteria in the upper GI tract
- There is 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)
- In addition, increased methane production, a gas by product of intestinal bacteria, has been associated with constipation predominant IBS (36)
- There are studies that present conflicting data, and therefore further studies are warrented to support this association

PATHOPHYSIOLOGY OF IBS-FOOD SESITIVITY

- 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)
  - Studies focusing on IgG antibodies have shown that eliminating specific foods in patients with IBS who have elevated IgG titers associated with those foods may reduce gastrointestinal symptoms
- **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 possibly inflammation (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 and/or fructans improved symptoms in patients with IBS who had been selected because of prior response to dietary change (40)

- **Gluten sensitivity**
  - A study suggested that in patients without villous atrophy, the presence of serum IgG antigliadin antibodies and expression of HLA-DQ2 may predict response to a gluten free diet in patients with diarrhea-predominant IBS (41)
  - A study in patients with irritable bowel syndrome with diarrhea without celiac disease found that dietary gluten altered small intestinal permeability and had a greater effect on bowel movement frequency in patients who were HLA-DQ2/8 positive compared with those who were HLA-DQ2/8 negative (42)

PATHOPHYSIOLOGY OF IBS-GENETICS

- Familial studies suggest a modest contribution of genetics to the development of IBS [90]
- Concordance rates for IBS in monozygotic twins ranged from 2 to 22 percent and rates in dizygotic twins ranged from 1 to 9 percent in one study (43), however, other studies demonstrate no difference in concordance rates
- Astudy found that having a parent with IBS was a greater independent predictor of IBS than having an affected twin, suggesting IBS could be due to social learning in addition to genetics (44)
- Genotyping studies have shown an association between IBS and polymorphisms in the serotonin transporter gene, resulting in altered serotonin reuptake efficacy that affects intestinal peristalsis (45) however, other studies show no such association
- Data suggests IBS patients may be genetically predisposed to an altered pattern of anti-inflammatory cytokine interleukin production, supporting the role of inflammation with the disorder (46)

PATHOPHYSIOLOGY OF IBS-PSYCHOSOCIAL DYSFUNCTION

- In one study, patients with IBS symptoms reported more lifetime and daily stressful events than control groups (47)
- 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), a peptide released from the paraventricular nucleus and considered to be a major mediator of the stress response
- Data suggests that overactivity in the brain CRF and CRF-receptor signaling system contributes to anxiety disorders and depression (49)
- A study reports IV administration of CRF increase abdominal pain and colonic motility in IBS patients to a higher degree than normal controls (50)

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); and in select cases, lactose and gluten avoidance
- In a randomized trial individuals with documented IBS were assigned to a low FODMAP diet or a more traditional IBS diet (regular meal pattern; 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)
    - A significant reduction in IBS symptom severity were documented in both dietary groups
- Patients with IBS should be advised to exclude foods that increase flatulence (eg, beans, onions, celery, carrots, raisins, bananas, apricots, prunes, Brussels sprouts, wheat germ, pretzels, and bagels)

Characteristics and sources of common FODMAPs

F	**Fermentable**		
O	**Oligosaccharides**	Fructans, galacto-oligosaccharides	Wheat, barley, rye, onion, leek, white part of spring onion, garlic, shallots, artichokes, beetroot, fennel, peas, chicory, pistachio, cashews, legumes, lentils, and chickpeas
D	**Disaccharides**	Lactose	Milk, custard, ice cream, and yogurt
M	**Monosaccharides**	"Free fructose" (fructose in excess of glucose)	Apples, pears, mangoes, cherries, watermelon, asparagus, sugar snap peas, honey, high-fructose corn syrup
A	**And**		
P	**Polyols**	Sorbitol, mannitol, maltitol, and xylitol	Apples, pears, apricots, cherries, nectarines, peaches, plums, watermelon, mushrooms, cauliflower, artificially sweetened chewing gum and confectionery

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TREATMENT-DIETARY MODIFICATIONS-LACTOSE AVOIDANCE

- An empiric trial of a lactose-free diet should be considered in patients who complain of persistent abdominal bloating despite exclusion of gas-producing foods
- Lactose intolerance can be confirmed with breath testing in patients who do not want to be on a lactose-restricted diet in the long term without clear evidence of malabsorption
- 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 (ie cow milk protein) and may tolerate milk from other mammals or other milks (soy, cashew, almond)
- Although the incidence of lactose malabsorption is not higher in patients with IBS, it has been demonstrated that patients with IBS and lactose intolerance have an exaggerated symptom response to lactose ingestion (52)

TREATMENT-DIETARY MODIFICATIONS-GLUTEN FREE

- A two-week trial of a gluten-free diet is suggested in patients with diarrhea-predominant IBS (IBS-D) with significant abdominal bloating and 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 1, however it does not alter transit or histology, and does not alter colonic permeability)
- In a randomized trial, 34 patients with no evidence of celiac disease (HLA-DQ2 and HLA-DQ8 negative or normal duodenal biopsies) were assigned to a gluten-containing diet or placebo for six weeks (53)
    - Patients documented more symptoms on a gluten-containing diet as compared with placebo (68 versus 40 percent)

TREATMENT-DIETARY MODIFICATIONS-FIBER

- The role of fiber in patients with IBS is controversial, but given the absence of serious side effects and potential benefit, psyllium should be considered in patients with IBS whose predominant symptom is constipation
- A starting dose of psyllium is one-half to one tablespoon daily
- A meta-analysis of pooled data from multiple trials used a combined endpoint for abdominal pain and global IBS symptoms and demonstrated that in six trials, psyllium was associated with a small improvement in symptoms compared to placebo (53)

TREATMENT-PHYSICAL ACTIVITY

- Physical activity should be encouraged in patients with IBS given a potential benefit with regard to IBS symptoms
- In a randomized trial, 102 patients with IBS were assigned to increased physical activity or maintenance of current activity levels (54)
  - Increased physical activity composed 20 to 60 minutes of moderate to vigorous activity three to five days per week
  - Seventy-five patients completed the study (38 in the physical activity arm and 37 in the control arm)
  - After 12 weeks, there was a trend toward more patients in the physical activity arm showing clinical improvement in the severity of IBS symptoms as compared with the control group (43 versus 26 percent, $p = 0.07$)
  - In addition, patients in the physical activity arm were significantly less likely to have worsening of their IBS symptoms as compared with controls (8 versus 23 percent)

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: IBS-CONSTIPATION

- In patients with I (IBS-C) who have failed a trial of soluble fiber polyethylene glycol (PEG) is suggested
- PEG is inexpensive, widely available, and has fewer side effects compared to other osmotic laxatives (ie lactulose, milk of magnesia)
  - 17 g of powder dissolved in 8 ounces of water once 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, however, there was no significant difference in the severity of bloating or abdominal pain (55)

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: IBS-CONSTIPATION

- Lubiprostone (Amitiza) is a locally acting chloride channel activator that enhances chloride-rich intestinal fluid secretion
- Lubiprostone is used for treatment of IBS-C in women 18 years and older
- The approved dose for IBS-C (8 micrograms BID) is lower than the approved dose for treatment of chronic idiopathic constipation (24 ug BID for CIC and opioid induced constipation)
- Lubiprostone has not been directly compared with other treatment options for IBS-C, and its long-term safety remains to be established
- Efficacy of lubiprostone has been demonstrated in two randomized trials in which the majority of patients were women
    - 1154 adults (92 percent women) with IBS and constipation were randomly assigned to lubiprostone (8 micrograms twice daily) vs placebo for 12 weeks
    - Patients randomized to lubiprostone were significantly more likely to achieve an overall response (18 versus 10 percent)
    - most common adverse event 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

- **Linaclotide** is a guanylate cyclase agonist that stimulates intestinal fluid secretion and transit
- Linaclotide is used for treatment of IBS-C at a dose of 290 micrograms daily
- The efficacy of linaclotide in the treatment of IBS-C has been demonstrated in two randomized controlled phase III trials
- In one randomized controlled trial, 800 patients with IBS-C were assigned to linaclotide (266 micrograms daily) or placebo for 12 weeks followed by a four-week withdrawal period
  - After 12 weeks, the percentage of patients meeting the composite endpoint (decrease of abdominal pain and increase of bm) was significantly greater with linaclotide compared to placebo (34 versus 21 percent)
  - Patients who received linaclotide also demonstrated a significant improvement in secondary endpoints of abdominal pain/discomfort, bloating, straining, stool consistency, number of bowel movements per week, compared to placebo
  - After the initial 12 weeks, patients originally given linaclotide and who remained on linaclotide showed sustained improvement in abdominal pain, but patients who were switched to placebo experienced recurrence of abdominal pain
  - Patients initially randomized to placebo had significant improvement in abdominal pain within one week after being switched to linaclotide
  - Diarrhea was the most common side effect, causing discontinuation of treatment in 5.7 percent of patients treated with linaclotide as compared with 0.3 percent 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 versus 14 percent)
- Long-term risks of linaclotide are unknown

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: IBS-DIARRHEA

- Initial treatment of IBSD is **loperamide** 2 mg 45 minutes before a meal on regularly scheduled doses
- Antidiarrheal agents inhibit peristalsis, prolong transit time, and reduce fecal volume
- Loperamide should not be used in patients with IBS-C and should be used in limited doses, on an as-needed basis, in patients with alternating diarrhea and constipation (maximum daily dose 16 mg/day)
- Loperamide is the only antidiarrheal agent evaluated in randomized trials in patients with IBS-D
- 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)

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: IBS-DIARRHEA

- Eluxadoline (Viberzi) is an agent that combines a mu-opioid receptor agonist and a delta-opioid receptor antagonist; it has been approved for treatment of IBS-D
- In two phase 3 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)
  - The primary endpoint was the proportion of patients who had a composite response of decrease in abdominal pain and improvement in stool consistency on the same day, for at least 50 percent of the days from weeks 1 through 12 and from weeks 1 through 26
  - For weeks 1 through 26, a significantly higher proportion of patients receiving eluxadoline (100 mg twice daily) achieved the primary endpoint as compared with placebo in both trials (29 versus 19 percent; 33 versus 20 percent)
  - The most common adverse events associated with eluxadoline were nausea, constipation, and abdominal pain

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: IBS-DIARRHEA

- In patients with persistent diarrhea despite antidiarrheals bile acid sequestrants (ie cholestyramine, colestipol, colesevelam) are recommended
- Use is limited by associated gastrointestinal side effects including bloating, flatulence, abdominal discomfort, and constipation
- The rationale for the use of bile acid sequestrants in patients with IBS-D is that up to 50 percent of 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) or placebo, treatment with colesevelam decreased colonic transit time with an average delay of four hours as compared with placebo (62)

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: IBS-DIARRHEA

- **Alosetron (Lotronex)**, a 5-hydroxytryptamine-3 receptor (5HT-3) antagonist, is approved for the treatment of severe diarrhea-predominant IBS in female patients whose symptoms have lasted for six months and who have failed to respond to all other conventional treatment
- Alosetron modulates visceral afferent activity from the gastrointestinal 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, alosetron or cilansetron resulted in a global improvement in IBS symptoms and relief of abdominal pain and discomfort (63)
- Side effects of ischemic colitis and complications of severe constipation led to the withdrawal of alosetron from the market in the United States
- After evaluation of postmarketing data, alosetron is now available in the United States but can be prescribed under restricted conditions, at a lower starting dose than previously approved, and by physicians enrolled in the alosetron prescribing program, and is approved for female patients exclusively

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: ABDOMINAL PAIN AND BLOATING

- Antispasmodics should be used on an as-needed basis
- In patients with IBS with constipation, initiate antispasmodics only if the abdominal pain persists despite treatment of constipation
- In patients with persistent abdominal pain despite antispasmodics, a trial of antidepressant therapy is advocated
- In patients with moderate to severe IBS without constipation, particularly those with bloating, who have failed to respond to other therapies, a two-week trial of **rifaximin (Xifaxan)** is suggested

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: ABDOMINAL PAIN AND BLOATING

- Antispasmodics include those that directly affect intestinal smooth muscle relaxation (ie mebeverine and pinaverine), and those that act via their anticholinergic or antimuscarinic properties (ie dicyclomine and hyoscyamine)
- The selective inhibition of gastrointestinal smooth muscle by antispasmodics and peppermint oil reduce stimulated colonic motor activity and may be beneficial in patients with postprandial abdominal pain, gas, bloating, and fecal urgency
- In a 2011 meta-analysis, antispasmodics were associated with a significant improvement in abdominal pain, global assessment and symptom score as compared with placebo
- Subgroup analyses demonstrated statistically significant benefits for cimetropium/dicyclomine, peppermint oil, pinaverium, and trimebutine (64)
- 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, also slow intestinal transit time, which may provide benefit in diarrhea-predominant IBS
- Given their effect on intestinal transit, TCAs should be used cautiously in patients with constipation
- For the treatment of abdominal pain in IBS, antidepressants should be started at low doses
- Due to the delayed onset of action of antidepressants, 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
- Desipramine should be started at a dose of 12.5 to 25 mg at bedtime
- If the patient is intolerant of one TCA, another may be tried

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)
- Furthermore, 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 pain, chronic D and depression
- SNRI (serotonin norepinephrine reuptake inhibitor) (duloxetine [Cymbalta], venlafaxine, desvenlafaxine)
  - NE and serotonin receptor uptake inhibitions
  - Effective with pain, anxiety and depression
- SSRI (selective serotonin reuptake inhibitors) (fluoxetine [Prozac], paroxitine [Paxil], citalopram [Celexa])
  - Serotonin reuptake inhibition
  - Effective with constipation, anxiety and depression

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: ABDOMINAL PAIN AND BLOATING

- **Antibiotics** should not be routinely recommended in all patients with IBS, in patients with 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 as compared with placebo (OR 1.55) (66)
- 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 as compared with those treated with placebo
- In these trials, 1260 patients with IBS without constipation were assigned to receive either rifaximin 550 mg three times daily or placebo for a total of 14 days and were then followed for 10 weeks (67)
    - Those who received rifaximin were more likely to report adequate relief of global IBS symptoms than patients who received placebo (41 versus 32 percent),relief of bloating (40 versus 30 percent) and an improvement in daily stool consistency (76 versus 66 percent)

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
- Only preliminary evidence exists for most probiotic health claims
- Even for the most studied strains, few have been sufficiently developed in basic and clinical research to warrant approval for health claim status to a regulatory agency such as the Food and Drug Administration or European Food Safety Authority, and to date, no claims have been approved by those two agencies

TREATMENT-ADJUNCTIVE PHARMACOLOGIC THERAPY: REFRACTORY SYMPTOMS

- Patients with continued symptoms despite adjunctive pharmacologic therapy mandate a careful reassessment
  - Compliance with medications?
  - Presence of alarm features?
  - 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 (eg, 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
- In a randomized trial of 60 patients, the use of ketotifen for eight weeks increased the threshold for discomfort with rectal distension in patients who were hypersensitive to rectal balloon distension at baseline, but not in those with normal sensitivity at baseline (68)
  - While there was a suggestion of symptom improvement in patients who received ketotifen as compared with those who received placebo, the results did not reach statistical significance

REFERENCES

1. Epidemiology of colonic symptoms and the irritable bowel syndrome. Talley NJ, Zinsmeister AR, Van Dyke C, Melton LJ 3rD *Gastroenterology*. 1991;101(4):927
2. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects.Hungin AP, Whorwell PJ, Tack J, Mearin F SO *Aliment Pharmacol Ther.* 2003;17(5):643
3. An evidence-based position statement on the management of irritable bowel syndrome. American College of Gastroenterology Task Force on Irritable Bowel Syndrome, Brandt LJ, Chey WD, Foxx-Orenstein AE, Schiller LR, Schoenfeld PS, Spiegel BM, Talley NJ, Quigley EM *Am J Gastroenterol*. 2009;104 Suppl 1:S1
4. Irritable bowel syndrome in office-based practice in the United States. Everhart JE, Renault PF *Gastroenterology*. 1991;100(4):998
5. The burden of selected digestive diseases in the United States. Sandler RS, Everhart JE, Donowitz M, Adams E, Cronin K, Goodman C, Gemmen E, Shah S, Avdic A, Rubin R *Gastroenterology*. 2002;122(5):1500
6. Nongastrointestinal symptoms of irritable bowel syndrome: an office-based clinical survey. Hershfield NB Can J Gastroenterol. 2005;19(4):231
7. Towards positive diagnosis of the irritable bowel. Manning AP, Thompson WG, Heaton KW, Morris AF *Br Med J*. 1978;2(6138):653
8. Bowel Disorders. Mearin F, Lacy BE, Chang L, Chey WD, Lembo AJ, Simren M, Spiller R *Gastroenterology*. 2016 Feb
9. 9. An evidence-based position statement on the management of irritable bowel syndrome. American College of Gastroenterology Task Force on Irritable Bowel Syndrome, Brandt LJ, Chey WD, Foxx-Orenstein AE, Schiller LR, Schoenfeld PS, Spiegel BM, Talley NJ, Quigley EM Am J Gastroenterol. 2009;104 Suppl 1:S1
10. 10. Abnormal propagation pattern of duodenal pressure waves in the irritable bowel syndrome (IBS) [correction of (IBD)]. Simrén M, Castedal M, Svedlund J, Abrahamsson H, Björnsson E Dig Dis Sci. 2000;45(11):2151
11. 11. Patients with irritable bowel syndrome have greater pain tolerance than normal subjects. Cook IJ, van Eeden A, Collins SM Gastroenterology. 1987;93(4):727
12. 12. Perception of electrocutaneous stimuli in irritable bowel syndrome. Iovino P, Tremolaterra F, Consalvo D, Sabbatini F, Mazzacca G, Ciacci C Am Gastroenterol. J 2006;101(3):596
13. 13. Relationship of abdominal bloating to distention in irritable bowel syndrome and effect of bowel habit. Houghton LA, Lea R, Agrawal A, Agrawal A, Reilly B, Whorwell PJ Gastroenterology. 2006;131(4):1003
14. 14. The role of intestinal gas in functional abdominal pain. Lasser RB, Bond JH, Levitt MD N Engl J Med. 1975;293(11):524
15. 15. Lipid-induced intestinal gas retention in irritable bowel syndrome. Serra J, Salvioli B, Azpiroz F, Malagelada JR Gastroenterology. 2002;123(3):700

REFERENCES

16. The development and maintenance of human visceral pain hypersensitivity is dependent on the N-methyl-D-aspartate receptor. Willert RP, Woolf CJ, Hobson AR, Delaney C, Thompson DG, Aziz Q *Gastroenterology*. 2004;126(3):683

17. Activation of the mucosal immune system in irritable bowel syndrome. Chadwick VS, Chen W, Shu D, Paulus B, Bethwaite P, Tie A, Wilson I *Gastroenterology*. 2002;122(7):1778

18. Full-thickness biopsy of the jejunum reveals inflammation and enteric neuropathy in irritable bowel syndrome.Törnblom H, Lindberg G, Nyberg B, Veress B Gastroenterology. 2002;123(6):1972

19. Increased faecal serine protease activity in diarrhoeic IBS patients: a colonic lumenal factor impairing colonic permeability and sensitivity. Gecse K, Róka R, Ferrier L, Leveque M, Eutamene H, Cartier C, Ait-Belgnaoui A, Rosztóczy A, Izbéki F, Fioramonti J, Wittmann T, Bueno L Gut. 2008;57(5):591

20. Diarrhoea-predominant IBS patients show mast cell activation and hyperplasia in the jejunum. Guilarte M, Santos J, de Torres I, Alonso C, Vicario M, Ramos L, Martínez C, Casellas F, Saperas E, Malagelada JR Gut. 2007;56(2):203

21. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome.Barbara G, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, Santini D, Pasquinelli G, Morselli-Labate AM, Grady EF, Bunnett NW, Collins SM, Corinaldesi R Gastroenterology. 2004;126(3):693

22. Immune activation in patients with irritable bowel syndrome. Liebregts T, Adam B, Bredack C, Röth A, Heinzel S, Lester S, Downie-Doyle S, Smith E, Drew P, Talley NJ, Holtmann G Gastroenterology. 2007;132(3):913

23. Bacillary dysentery as a causative factor of irritable bowel syndrome and its pathogenesis. Wang LH, Fang XC, Pan GZ Gut. 2004;53(8):1096

24. Postinfectious irritable bowel syndrome--a meta-analysis. Halvorson HA, Schlett CD, Riddle MS Am J Gastroenterol. 2006;101(8):1894.\

25. Systematic review and meta-analysis: The incidence and prognosis of post-infectious irritable bowel syndrome. Thabane M, Kottachchi DT, Marshall JK Aliment Pharmacol Ther. 2007;26(4):535

26. Postinfective diarrhoea and bile acid malabsorption. Niaz SK, Sandrasegaran K, Renny FH, Jones BJ J R Coll Physicians Lond. 1997;31(1):53

27. Increased rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following acute Campylobacter enteritis and in post-dysenteric irritable bowel syndrome.Spiller RC, Jenkins D, Thornley JP, Hebden JM, Wright T, Skinner M, Neal KR Gut. 2000;47(6):804

28. Randomized, double-blind, placebo-controlled trial of prednisolone in post-infectious irritable bowel syndrome. Dunlop SP, Jenkins D, Neal KR, Naesdal J, Borgaonker M, Collins SM, Spiller RC Aliment Pharmacol Ther. 2003;18(1):77

REFERENCES

29. Relative importance of enterochromaffin cell hyperplasia, anxiety, and depression in postinfectious IBS. Dunlop SP, Jenkins D, Neal KR, Spiller RC *Gastroenterology*. 2003;125(6):1651

30. Gastrointestinal symptoms after infectious diarrhea: a five-year follow-up in a Swedish cohort of adults. Törnblom H, Holmvall P, Svenungsson B, Lindberg G *Clin Gastroenterol* Hepatol. 2007;5(4):461

31. The fecal microbiota of irritable bowel syndrome patients differs significantly from that of healthy subjects. Kassinen A, Krogius-Kurikka L, Mäkivuokko H, RinttiläT, Paulin L, Corander J, Malinen E, Apajalahti J, Palva A *Gastroenterology*. 2007;133(1):24

32. The hypersensitivity to colonic distension of IBS patients can be transferred to rats through their fecal microbiota. Crouzet L, Gaultier E, Del'Homme C, Cartier C, Delmas E, Dapoigny M, Fioramonti J, Bernalier-Donadille A *Neurogastroenterol Motil*. 2013 Apr;25(4):e272-82. Epub 2013 Feb 25

33. Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritabl e bowel syndrome. Nobaek S, Johansson ML, Molin G, AhrnéS, Jeppsson B *Am J Gastroenterol*. 2000;95(5):1231

34. Hydrogen glucose breath test to detect small intestinal bacterial overgrowth: a prevalence case-control study in irritable bowel syndrome. Lupascu A, Gabrielli M, Lauritano EC, Scarpellini E, Santoliquido A, Cammarota G, Flore R, Tondi P, Pola P, Gasbarrini G, Gasbarrini A Aliment Pharmacol Ther. 2005;22(11-12):1157

35. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. Pimentel M, Chow EJ, L in HC *Am J Gastroenterol*. 2000;95(12):3503

36. The degree of breath methane production in IBS correlates with the severity of constipation. Chatterjee S, Park S, Low K, Kong Y, Pimentel M Am J Gastroenterol. 2007;102(4):837

37. Food intolerance and skin prick test in treated and untreated irritable bowel syndrome. Jun DW, Lee OY, Yoon HJ, Lee SH, Lee HL, Choi HS, Yoon BC, Lee MH, Lee DH, Cho SH World J Gastroenterol. 2006;12(15):2382

38. The irritable bowel syndrome and food hypersensitivity. Zwetchkenbaum J, Burakoff R Ann Allergy. 1988;61(1):47

39. Personal view: food for thought--western lifestyle and susceptibility to Crohn's disease. The FODMAP hypothesis. Gibson PR, Shepherd SJ Aliment Pharmacol Ther. 2005;21(12):1399

40. Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomized placebo-controlled evidence. Shepherd SJ, Parker FC, Muir JG, Gibson PR Clin Gastroenterol Hepatol. 2008;6(7):765

41. Predictors of clinical response to gluten-free diet in patients diagnosed with diarrhea-predominant irritable bowel syndrome. Wahnschaffe U, Schulzke JD, Zeitz M, Ullrich RClin Gastroenterol Hepatol. 2007;5(7):844

42. A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: effects on bowel frequency and intestinal function. Vazquez-Roque MI, Camilleri M, Smyrk T, Murray JA, Marietta E, O'Neill J, Carlson P, Lamsam J, Janzow D, Eckert D, Burton D, Zinsmeister AR Gastroenterology. 2013 May;144(5):903-911.e3. Epub 2013 Jan 25

43. Irritable bowel syndrome in twins: heredity and social learning both contribute to etiology. Levy RL, Jones KR, Whitehead WE, Feld SI, Talley NJ, Corey LA Gastroenterology. 2001;121(4):799

REFERENCES

44. Irritable bowel syndrome in twins: heredity and social learning both contribute to etiology. Levy RL, Jones KR, Whitehead WE, Feld SI, Talley NJ, Corey LA *Gastroenterology*. 2001;121(4):799

45. Association of distinct alpha(2) adrenoceptor and serotonin transporter polymorphisms with constipation and somatic symptoms in functional gastrointestinal disorders. Kim HJ, Camilleri M, Carlson PJ, Cremonini F, Ferber I, Stephens D, McKinzie S, Zinsmeister AR, Urrutia R *Gut.* 2004;53(6):829

46. Interleukin 10 genotypes in irritable bowel syndrome: evidence for an inflammatory component? Gonsalkorale WM, Perrey C, Pravica V, Whorwell PJ, Hutchinson IV *Gut.* 2003;52(1):91

47. Psychosocial factors are linked to functional gastrointestinal disorders: a population based nested case-control study. Locke GR 3rd, Weaver AL, Melton LJ 3rd, Talley NJ Am J Gastroenterol. 2004;99(2):350

48. Psychosocial risk markers for new onset irritable bowel syndrome--results of a large prospective population-based study. Nicholl BI, Halder SL, Macfarlane GJ, Thompson DG, O'Brien S, Musleh M, McBeth J Pain. 2008;137(1):147

49.Hyperactivity of CRH neuronal circuits as a target for therapeutic interventions in affective disorders. Keck ME, Holsboer F Peptides. 2001;22(5):835

50. Impact of corticotropin-releasing hormone on gastrointestinal motility and adrenocorticotropic hormone in normal controls and patients with irritable bowel syndrome. Fukudo S, Nomura T, Hongo M Gut. 1998;42(6):845

51. Diet low in FODMAPs reduces symptoms of irritable bowel syndrome as well as traditional dietary advice: a randomized controlled trial. Böhn L, Störsrud S, Liljebo T, Collin L, Lindfors P, Törnblom H, Simrén M Gastroenterology. 2015;149(6):1399

52. Bloating and distention in irritable bowel syndrome: the role of gas production and visceral sensation after lactose ingestion in a population with lactase deficiency. Zhu Y, Zheng X, Cong Y, Chu H, Fried M, Dai N, Fox M Am J Gastroenterol. 2013;108(9):1516

53. Irritable bowel syndrome. Ford AC, Talley NJ BMJ. 2012;345:e5836

54. Physical activity improves symptoms in irritable bowel syndrome: a randomized controlled trial. Johannesson E, Simrén M, Strid H, Bajor A, Sadik R Am J Gastroenterol. 2011;106(5):915

55. Randomized clinical trial: macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. Chapman RW, Stanghellini V, Geraint M, Halphen M Am J Gastroenterol. 2013;108(9):1508

56. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome--results of two randomized, placebo-controlled studies. Drossman DA, Chey WD, Johanson JF, Fass R, Scott C, Panas R, Ueno R Aliment Pharmacol Ther. 2009;29(3):329

57. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. Rao S, Lembo AJ, Shiff SJ, Lavins BJ, Currie MG, Jia XD, Shi K, MacDougall JE, Shao JZ, Eng P, Fox SM, Schneier HA, Kurtz CB, Johnston JM Am J Gastroenterol. 2012;107(11):1714

REFERENCES

58. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. Chey WD, Lembo AJ, Lavins BJ, Shiff SJ, Kurtz CB, Currie MG, MacDougall JE, Jia XD, Shao JZ, Fitch DA, Baird MJ, Schneier HA, Johnston JM *Am J Gastroenterol.* 2012;107(11):1702

59. Loperamide treatment of the irritable bowel syndrome. Hovdenak N *Scand J Gastroenterol* Suppl. 1987;130:81

60. Eluxadoline for Irritable Bowel Syndrome with Diarrhea Anthony J. Lembo, M.D., Brian E. Lacy, M.D., Ph.D., Marc J. Zuckerman, M.D., Ron Schey, M.D., Leonard S. Dove, Ph.D., David A. Andrae, Ph.D., J. Michael Davenport, Ph.D., Gail McIntyre, Ph.D., Rocio Lopez, Ph.D., Lisa Turner, R.Ph., and Paul S. Covington, M.D. *N Engl J Med* 2016; 374:242-253January 21, 2016DOI: 10.1056/NEJMoa1505180

61. Systematic review: the prevalence of idiopathic bile acid malabsorption as diagnosed by SeHCAT scanning in patients with diarrhoea-predominant irritable bowel syndrome. Wedlake L, A'Hern R, Russell D, Thomas K, Walters JR, Andreyev HJ *Aliment Pharmacol Ther.* 2009 Oct;30(7):707-17. Epub 2009 Jun 30

62. Effects of chenodeoxycholate and a bile acid sequestrant, colesevelam, on intestinal transit and bowel function. Odunsi-Shiyanbade ST, Camilleri M, McKinzie S, Burton D, Carlson P, Busciglio IA, Lamsam J, Singh R, Zinsmeister *ARClin Gastroenterol Hepatol.* 2010 Feb;8(2):159-65. Epub 2009 Oct 30

63. Effects of 5-hydroxytryptamine (serotonin) type 3 antagonists on symptom relief and constipation in nonconstipated irritable bowel syndrome: a systematic review and meta-analysis of randomized controlled trials. Andresen V, Montori VM, Keller J, West CP, Layer P, Camilleri M *Clin Gastroenterol Hepatol.* 2008;6(5):545

64. Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. Ruepert L, Quartero AO, de Wit NJ, van der Heijden GJ, Rubin G, Muris JW Cochrane Database Syst Rev. 2011

65. Efficacy and Safety of Antidepressants for the Treatment of Irritable Bowel Syndrome: A Meta-Analysis. Xie C, Tang Y, Wang Y, Yu T, Wang Y, Jiang L, Lin L PLoS One. 2015;10(8):e0127815. Epub 2015

66. The efficacy and safety of rifaximin for the irritable bowel syndrome: a systematic review and meta-analysis. Menees SB, Maneerattannaporn M, Kim HM, Chey WD *Am J Gastroenterol.* 2012;107(1):28

67. Rifaximin therapy for patients with irritable bowel syndrome without constipation.Pimentel M, Lembo A, Chey WD, Zakko S, Ringel Y, Yu J, Mareya SM, Shaw AL, Bortey E, Forbes WP, TARGET Study Group N Engl J Med. 2011;364(1):22

68. The mast cell stabiliser ketotifen decreases visceral hypersensitivity and improves intestinal symptoms in patients with irritable bowel syndrome. Klooker TK, Braak B, Koopman KE, Welting O, Wouters MM, van der Heide S, Schemann M, Bischoff SC, van den Wijngaard RM, Boeckxstaens GE Gut. 2010;59(9):1213

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