



GHAPP

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Diagnosis and Management of IBS-D

Kimberly Orleck, PA-C
Atlanta Gastroenterology Associates
Atlanta, GA

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Disclosures

Kimberly Orleck, PA-C

Speakers Bureau: Abbvie, Janssen, Salix

Consultant: Bristol Myers Squibb, Abbvie,
Phathom Pharmaceuticals, Salix

Definitions








- Irritable Bowel Syndrome
 - Chronic disorder of brain gut interaction
 - Aka functional GI disorder
 - Absence of organic disease
 - Characterized by chronic abdominal pain and altered bowel habits
 - Abdominal pain is related to defecation
 - 3 main subtypes
 - IBS-C, IBS-D, IBS-M

Diagnosis

- Clinical diagnosis of IBS requires symptom based diagnostic criteria
- Rome IV Criteria
- Abdominal pain ≥ 1 day per week for the last 3 months associated with ≥ 2 of the following
 - Related to defecation
 - Change in frequency of stool
 - Change in form or appearance of stool
- Criteria should be fulfilled for the last 3 months with symptom onset ≥ 6 months before diagnosis

Diagnosis

- IBS-D
 - > 25% bowel movements are type 6 or 7 (loose or watery)
 - < 25% bowel movements are type 1 or 2 (hard or lumpy)

| | | |
|--------|---|--|
| Type 1 |  | Separate hard lumps, like nuts |
| Type 2 |  | Sausage-shaped but lumpy |
| Type 3 |  | Like a sausage but with cracks on the surface |
| Type 4 |  | Like a sausage or snake, smooth and soft |
| Type 5 |  | Soft blobs with clear-cut edges |
| Type 6 |  | Fluffy pieces with ragged edges, a mushy stool |
| Type 7 |  | Watery, no solid pieces. |

Diagnosis

- Thorough history
 - Make sure no alarming features
 - Hematochezia; anemia; age > 50; fever; nocturnal symptoms; unintentional weight loss, FH of celiac, IBD or colon CA
- Physical exam
 - Normal but can have abdominal tenderness
- Limited diagnostic testing

Diagnosis

- In the absence of **alarm features**, extensive diagnostic testing is NOT required to diagnose IBS
- These established symptom-based diagnostic criteria have a **98%** positive predictive value for IBS
- Therefore, IBS is not a diagnosis of exclusion, but a symptom-based diagnosis

Epidemiology

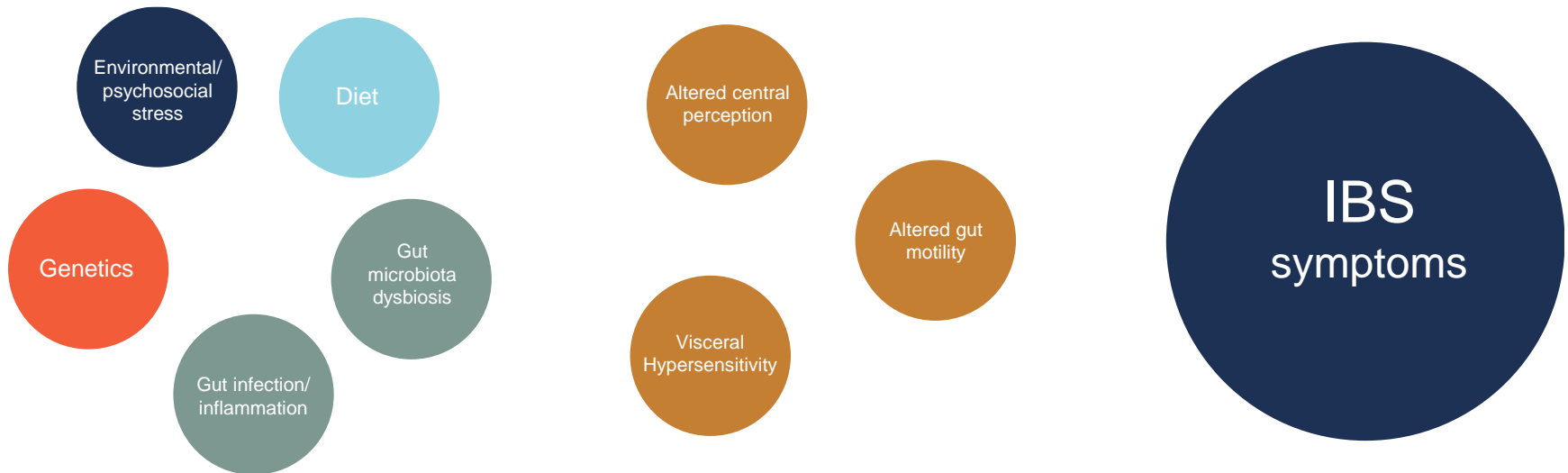
- Prevalence in the US is 10-15%
 - 40% of patients who meet the diagnostic criteria do not have a formal diagnosis
- Higher prevalence in females compared to males (almost twice as common)
- Increased incidence age < 50
- Associated with other common conditions
 - Anxiety, depression, fibromyalgia, functional dyspepsia, NCCP, chronic fatigue syndrome

Impact of IBS-D

- IBS accounts for 5-30% of all referrals to GI
- IBS is associated with increased health care costs
 - Direct costs associated with IBS in the US estimated to be as high as \$1.5-10 billion dollars per year (excluding OTC and prescription medications)
 - + indirect costs: negative effect on QOL, work productivity, absenteeism
- It is the second highest cause of work absenteeism
 - On average IBS patients miss 2 days of work/month and have 9 days or reduced work/month
- IBS has a significant impact on a patient's physical, emotional, and social life

Pathophysiology

The pathophysiology of IBS is multi-factorial



Pathophysiology

- Alterations in the gut microbiome
- Alterations in gastrointestinal motility and fluid secretion
- Abnormal visceral hypersensitivity
- Brain gut axis/Psychosocial factors
- Post infectious
 - More often seen in females, those who received ABX and those with overlapping anxiety and depression
 - Up to 41.9% develop post parasitic infection and 13.8% post bacterial infection
- Genetic predisposition
- ?Intestinal inflammation
- ?SIBO

Diagnosis

- **ACG guidelines**
- Rule out celiac disease in those with IBS-D symptoms
 - Strong recommendation, Moderate quality of evidence
 - Study in which 9,275 patients fulfilled IBS criteria and 2.6% with positive serology and 3.3% had biopsy proven celiac disease
 - Screen with IgA TTG and quantitative IgA level

Diagnosis

- Check either fecal calprotectin or fecal lactoferrin and CRP in suspected IBS-D
 - Fecal Calpro/CRP
 - Strong recommendation, moderate quality of evidence
 - FC sensitivity and sensitivity for IBD (compared to endoscopy) 93 and 96% retrospectively
 - CRP has highest utility diagnosing IBD of all serologic tests
 - » CRP < 5 yielded a 1% probability of IBD
 - Fecal lactoferrin
 - Strong recommendation, low quality of evidence
 - Fecal lactoferrin has a sensitivity/specificity of 67-86% and 96-100% for IBD

Diagnosis

- Recommend against checking stool studies for enteric pathogens in all IBS-D patients
 - Conditional recommendation; low quality of evidence
 - Consider testing for giardiasis if patient has risk factors
 - People/children in childcare settings
 - People who are in close contact with someone who has giardia
 - Travelers within areas that have poor sanitation
 - People who have contact with feces during sexual activity
 - Backpackers or campers who drink untreated water from springs, lakes, or rivers
 - Swimmers who swallow water from swimming pools, hot tubs, interactive fountains, or untreated recreational water from springs, lakes, or rivers
 - People who get their household water from a shallow well
 - People with weakened immune systems
 - People who have contact with infected animals or animal environments contaminated with feces

Diagnosis

- Recommend against routine colonoscopy in patients with IBS symptoms < 45 years of age without alarming features
 - Conditional recommendation; low quality of evidence
 - Ensure patients are up-to-date with screening independent of their IBS symptoms
 - Consider in women > 60 who are high risk for microscopic colitis
 - Polyp detection rate is lower in patients with IBS compared to healthy controls (7.7% vs 26.1%)

Diagnosis

- Recommend against food allergy or food sensitivity testing
 - Consensus recommendation; unable to assess using GRADE methodology
 - IBS patients are more likely to report adverse reactions to food (up to 50% of IBS pts) but true allergies are no more common in IBS patients
 - True food allergy occurs in 1-3% adults
 - IBS patients are not more likely than general population
 - Poor diagnostic tests
 - Most reactions are intolerances or sensitivities
 - Consider testing if there are reproducible symptoms concerning a food allergy (+ atopic individual)

Diagnosis

- ACG suggests that categorizing patients based on accurate IBS subtype improves patient therapy
 - Consensus recommendation, unable to assess using GRAED methodology
 - Considerations
 - More than 50% of IBS patients change subtype over a 1-year period
 - Categorize using BSFS
 - Determine using abnormal bowel movements when off therapies that can alter bowels
 - Daily diaries for 2 weeks helps increase accuracy of assessment

Diagnosis

- ACG recommends a positive diagnostic strategy as compared to a diagnostic strategy of exclusion
 - Strong recommendation, high quality of evidence
 - Symptom-based diagnosis has been shown to have a positive predictive value of 98%
 - A study looking at the economic burden of IBS-D (almost 40,000 patients) showed mean annual cost for IBS-D patients was over \$13,000, half of which was due to diagnostic testing, labs and radiology

Non-Pharmacologic Treatment Options

- ACG recommends limited trial of low FODMAP diet in patients with IBS to improve global symptoms
 - Conditional recommendation, very low quality of evidence
 - Most trials reported benefit, particularly of abdominal pain and bloating
 - Overall safe without AEs
 - Include all 3 phases of FODMAP
 - Utilize trained dietician

| Eliminate foods containing fodmaps | | | | |
|--|--|---|--|--|
| excess fructose | lactose | fructans | galactans | polyols |
| fruit apple, mango, nashi, pear, tinned fruit in natural juice, watermelon sweeteners fructose, high fructose corn syrup large total fructose dose concentrated fruit sources, large serves of fruit, dried fruit, fruit juice honey corn syrup, fruisana | milk milk from cows, goats or sheep, custard, ice cream, yoghurt cheeses soft unripened cheeses eg, cottage, cream, mascarpone, ricotta | vegetables asparagus, beetroot, broccoli, brussels sprouts, cabbage, eggplant, fennel, garlic, leek, okra, onion (all), shallots, spring onion cereals wheat and rye, in large amounts eg, bread, crackers, cookies, couscous, pasta fruit custard apple, persimmon, watermelon miscellaneous chicory, dandelion, inulin | legumes baked beans, chickpeas, kidney beans, lentils vegetables cauliflower, green capsicum (bell pepper), mushroom, sweet corn sweeteners sorbitol (420) mannitol (421) isomalt (953) maltitol (965) xylitol (967) | fruit apple, apricot, avocado, blackberry, cherry, lychee, nashi, nectarine, peach, pear, plum, prune, watermelon vegetables cauliflower, green capsicum (bell pepper), mushroom, sweet corn sweeteners sorbitol (420) mannitol (421) isomalt (953) maltitol (965) xylitol (967) |

Non-Pharmacologic Treatments



- ACG recommends that soluble fiber, but not insoluble, be used to treat global IBS symptoms
 - Strong recommendation, Moderate quality of evidence
 - Soluble fiber: psyllium, oat bran, barley and beans
 - In a systemic review of fiber in IBS including 15 RCTs of 946 pts fiber led to statistically significant benefit in IBS symptoms over placebo
 - More data with IBS-C
 - Insoluble fiber may exacerbate pain and bloating in IBS, and has no evidence for efficacy

Pharmacologic Treatment Options for IBS-D

Modulation of gut flora

- Rifaximin
- Probiotics

Antispasmodics

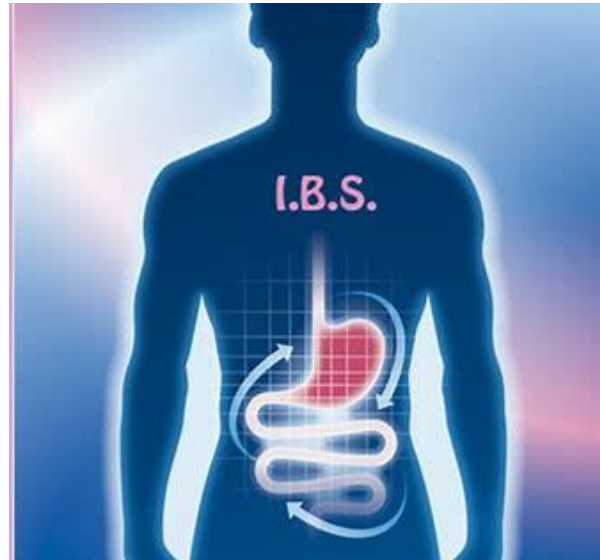
Peppermint oil

Opioid receptor modulators

- Loperamide (mu)
- Eluxadoline (mixed)

Antidepressants

TCAs



Bile acid binding agents

- Cholestyramine
- Colestid/Colesevelam

5-HT₃ antagonists

- Alosetron

Fiber supplements

Pharmacologic Treatments

- ACG recommends against the use of antispasmodics to treat global IBS
 - Conditional recommendation; low quality of evidence
 - Small studies show symptom improvement (? significance) but higher side effects compared to placebo
 - Limited data to support its use
 - Relatively safe but side effects common and limited data supporting their use
 - AEs up to 87% in studies
 - Most common AEs: dry mouth, constipation, blurry vision

Pharmacologic Treatments

- ACG recommends against probiotics for the treatment of global IBS symptoms
 - Conditional recommendation; very low level of evidence
 - Small studies, multiple types/strains, inconsistent benefit, lack of rigorous trials
 - Meta-analysis of > 4400 patients

Pharmacologic Treatments

- ACG recommends against the use of bile acid sequestrants to treat global IBS-D symptoms
 - Conditional recommendation, low level of evidence
 - Lack of widely available and reliable tests for bile acid malabsorption and adequately powered trials
- ACG recommends against the use of fecal transplant for the treatment of global IBS symptoms
 - Strong recommendation, very low level of evidence
 - No significant difference in IBS global symptoms with FMT vs placebo

Pharmacologic Treatments



- ACG recommends the use of peppermint to provide relief of global IBS symptoms
 - Conditional recommendation, Low quality of evidence
 - Small studies have shown decreased abdominal pain, discomfort and IBS severity
 - Meta-analysis of 12 RCTs of 735 patients showed response rates ranged from 34.4% in the (placebo) to 46.8% (small intestinal-release peppermint oil). There were significant differences, albeit minimal, in several secondary outcomes: abdominal pain, discomfort, and IBS severity

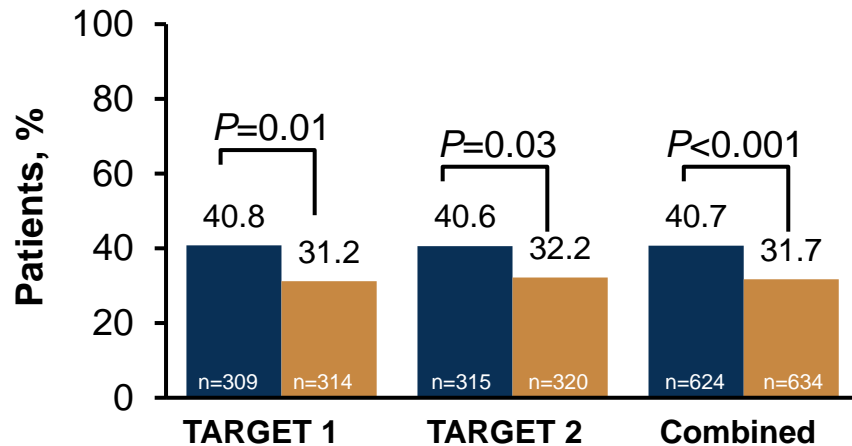
Pharmacologic Treatments

- ACG recommends the use of Rifaximin to treat global IBS-D symptoms
 - Strong recommendation; moderate level of evidence.
 - Trials show significant benefit over placebo
 - 40.8% of Rifaximin treated subjects had improvement in pain and stool consistency compared to 31.7% of placebo
 - 64% had relapse of symptoms but with re-treatment with rifaximin was superior to placebo again
 - Approval for IBS-D treatment with up to 2 additional treatments for symptom recurrence

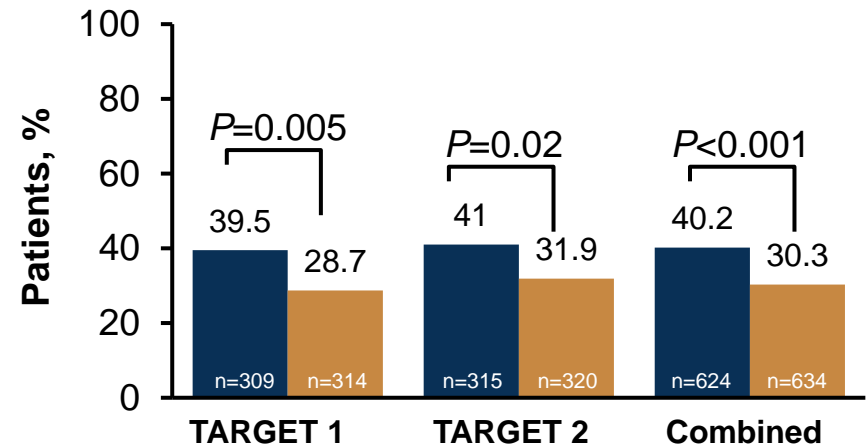
Rifaximin, a Nonabsorbable Antibiotic, Improves Global IBS Symptoms and Bloating in IBS-D

Outcomes at 4 Weeks

Adequate Relief of Global IBS Symptoms



Adequate Relief of IBS-Related Bloating



■ Rifaximin ■ Placebo

Pharmacologic Treatments

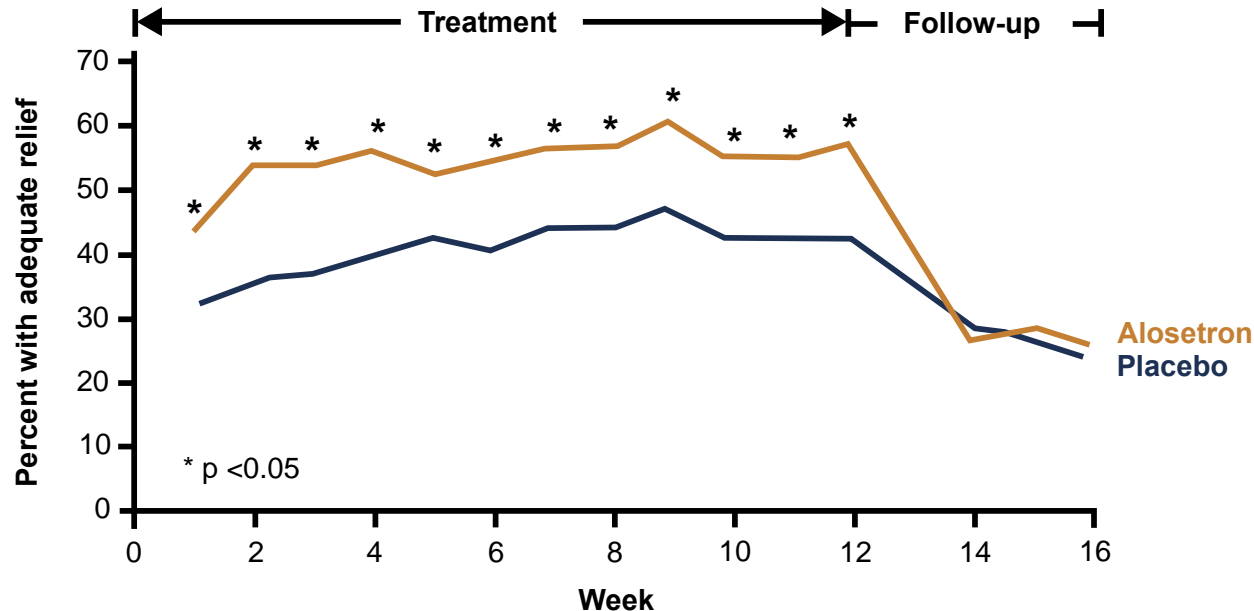
- ACG recommends the use alosetron to relieve global IBS-D symptoms in women with severe symptoms who have failed conventional therapy
 - Conditional recommendation; Low quality of evidence
 - Post-marketing reports of increased rates of ischemic colitis, complicated constipation and death and therefore withdrawn in 2000 but reintroduced under risk evaluation and mitigation strategy
 - Studies showed global improvement from 12.2-32% and overall response rate of 45%

Pharmacologic Treatments

Alosetron

- In both of the phase III placebo-controlled studies, alosetron was associated with a significant improvement in the proportion of women with pain relief during treatment (41 versus 29 percent and 41 versus 26 percent in the two studies, respectively)

Alosetron



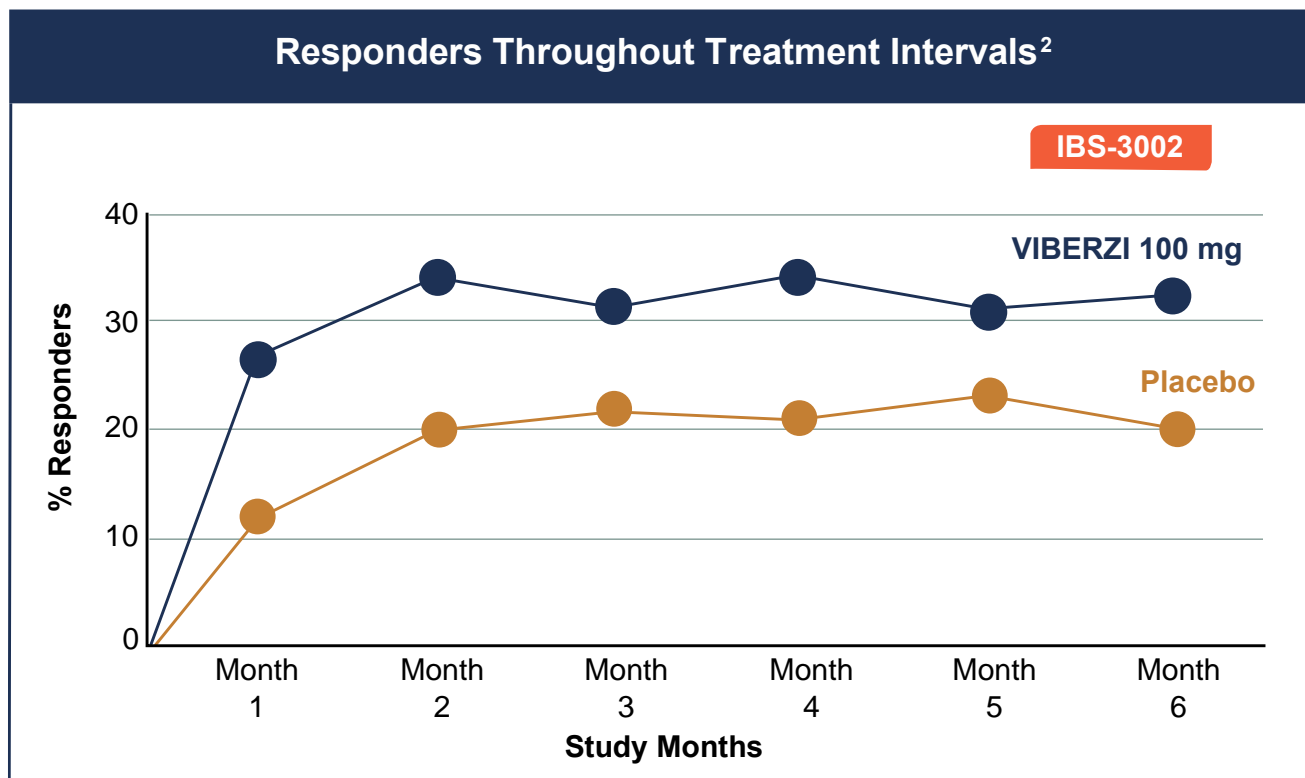
Results of a controlled trial of 647 women with IBS-D or IBS-M. Alosetron (1 mg BID) or placebo for 12 weeks. A significantly greater proportion of women treated with alosetron (41 verses 29 percent with placebo) described adequate relief of pain and discomfort during all three months of therapy. This difference disappeared with cessation of therapy.

Pharmacologic Treatments

- ACG recommends that mixed opioid agonists/antagonists should be used to treat global IBS-D symptoms
 - Conditional recommendation, moderate quality of evidence
 - Endpoint was significant decrease in abdominal pain (> 30% from baseline) and stool consistency score < 5 using BSFS
 - More likely to be met by patients on eluxadoline vs placebo
 - Most common AEs: constipation 8% and nausea 7.7%
 - Studies show proven benefit even in patients w IBS-D who failed to respond to loperamide
 - Loperamide is not recommended 1st line for IBS-D as it fails to improve global symptoms (may improve diarrhea)

Eluxadoline

The proportion of patients who were combined responders to VIBERZI at each 4-week interval was numerically higher than placebo as early as month 1 through month 6¹



Pharmacologic Treatments

- ACG recommends TCAs be used to treat global symptoms of IBS
 - Strong recommendation, moderate quality of evidence
 - Works to decrease visceral pain, slow motility and decrease psychological distress
 - Studies show patients treated with TCAs were 2X more likely to have improvement in global IBS symptoms compares with placebo
 - 42.7% of TCA receiving patients did not have global improvement in symptoms compared with 63.8% of placebo receiving patients did not have global improvement
 - AEs: dry mouth (36%), insomnia (24%), constipation (23%), flushing (23%), palpitations (9%), decreased appetite (8%)

Non-Pharmacologic Treatments

- ACG recommends that gut-directed psychotherapies be used to treat global IBS symptoms
 - Conditional recommendations; very low quality of evidence
 - Cognitive behavior therapy (CBT), GI and gut-directed hypnotherapy (GDH) improve IBS symptom severity by targeting the cognitive and affective factors known to drive IBS symptoms
 - Recommend gut-directed psychotherapies in conjunction with other IBS therapies for patients who are emotionally stable but who exhibit cognitive-affective drivers of IBS symptoms