



Beating the Bowel Blues: An Update on the Treatment of Irritable Bowel Syndrome

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Disclosures



- Matthew Nelson declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

Objectives



- At the conclusion of this program, the pharmacist will be able to:
 - Identify patients who present with symptoms consistent with a diagnosis of IBS
 - Compare the evidence supporting the use of the agents used to treat of IBS
 - Describe significant adverse events caused by medications in the treatment of IBS
 - Evaluate the appropriateness of IBS treatment based on the patient's presentation
 - Recommend therapy for IBS patients with persistent symptoms despite usual care

Pre-Test Question 1



- True or False: In the United States, irritable bowel syndrome is the most common disorder diagnosed by gastroenterologists.

Pre-Test Question 2



- Which of the following medication classes can exacerbate IBS symptoms?
 - a. Antihistamines
 - b. Antibiotics
 - c. NSAIDs
 - d. All of the above

Pre-Test Question 3



- Which of the following medications is indicated for treating IBS-D (Diarrhea predominant)?
 - a. Linaclotide
 - b. Rifaximin
 - c. Lubiprostone
 - d. Naloxegol

Pre-test Question 4



- Which of the following medications has a black box warning for severe constipation and ischemic colitis?
 - a. Alosetron
 - b. Linaclotide
 - c. Rifaximin
 - d. Eluxadoline

Irritable Bowel Syndrome



- IBS is a chronic functional bowel disorder characterized by:
 - Abdominal pain/ discomfort
 - Altered defecation
 - Other symptoms:
 - Bloating
 - Straining
 - Rectal urgency
 - Sensation of incomplete evacuation

Epidemiology



- Most commonly diagnosed GI condition
- Prevalence of about 10-15% in North America and 7-10% worldwide
- Affects twice as many females in North America
- Affects young adults more than elderly
- Cause of 25 – 50% of GI consults

Diagnosis



- Diagnosis based on presence of symptoms and exclusion of other organic disease
- Rome III criteria:
 - Presence of recurrent abdominal pain or discomfort for at least 3 days per month for the past 3 months associated with at least 2 of the following:
 - Improvement with defecation
 - Onset associated with a change in stool frequency
 - Onset associated with a change in appearance of stool
- Consider referral to a GI specialist any patient that has a chronic change in stool frequency associated with abdominal pain or discomfort

Alarm Signs/Symptoms



- Rectal bleeding
- Unintentional weight loss
- Family history of colon cancer
- Anemia
- Abdominal Mass
- Fever

IBS Classification



- IBS-C
 - Constipation predominant
- IBS-D
 - Diarrhea predominant
- IBS-M
 - Mixed pattern
 - Some resources will also refer to pain-predominant or un-subtyped IBS

Question 1



- Which of the following is NOT a condition that is consistent with the ROME-III criteria for the diagnosis of IBS?
 - a. Recurrent abdominal pain that improves after defecation
 - b. Recurrent abdominal pain that is associated with a reduced number of stools per day
 - c. Recurrent abdominal pain that is associated with loose stool
 - d. New onset abdominal pain for the past 2 weeks
- Feedback: D, abdominal pain or discomfort must be chronic over at least the past 3 months in order to meet the Rome III criteria for IBS

Pathophysiology



- Poorly understood
- Intestinal motor dysfunction or increased visceral sensitivity caused by alterations in:
 - Genetics
 - Motility factors
 - Inflammation
 - Colonic infections
 - Mechanical irritation to nerves
 - Stress or other psychological factors

Goals of Treatment



- Alleviate symptoms
- Minimize complications
- Decrease hospitalizations
- Enhance work productivity
- Improve quality of life

Non-pharmacologic Treatment



- Cognitive-behavioral therapy
- Avoid nutritionally depleted diet
- Eat regular meals
- Lactose restriction (if lactose intolerant)
- Avoid excessive fructose, sorbitol and mannitol
- Avoid caffeine and alcohol

Probiotics



- Significant heterogeneity amongst study results
- Guidelines support a weak recommendation for their use in IBS for improvement of global symptoms, bloating, and flatulence
- No recommendations regarding specific formulations can be made due to insufficient data

Treatments that can Exacerbate IBS



- Over-the-Counter

- Antihistamines
- Calcium
- Iron
- Magnesium
- Nonsteroidal anti-inflammatory drugs
- Wheat bran

- Prescription

- Antibiotics
- Antidepressants
- Antiparkinsonian drugs
- Antipsychotics
- Calcium-channel blockers
- Diuretics
- Metformin
- Opioids
- Sympathomimetics

Symptom-directed Pharmacotherapy



- IBS-C
 - Bulk-forming Laxatives
 - Antispasmodics
- IBS-D
 - Antidiarrheals
 - Antispasmodics

Fiber/Laxatives



- Increase dietary fiber (up to 20 gm/day)
- Maintain adequate fluid intake (2--3 L/day)
- Bulking agents
 - Psyllium, Methylcellulose
 - Increase water absorption into colon and stimulate peristaltic activity by increasing fecal bulk
 - Results in increased frequency of bowel movements w/o improvement in pain or bloating
 - Initial dose once daily with a meal, increase to 2-3 times daily with meals
 - ADRs: abdominal cramps, bloating, diarrhea
- Laxatives (milk of magnesia, lactulose, polyethylene glycol)
 - No evidence supporting use
 - If used, use at lowest dose for shortest duration possible

Antidiarrheals



- Delay transit of intraluminal contents
- Prolong contact time in gastrointestinal tract
 - Loperamide as needed
 - Diphenoxylate/atropine as needed
- Although the use of these agents may reduce the frequency of diarrhea, there is no evidence that they reduce global IBS symptoms (such as abdominal discomfort or pain)

Antispasmodics



- Peppermint oil
 - Relaxes gastrointestinal smooth muscle by reducing calcium influx
 - In successful studies an enteric-coated preparation of peppermint oil was employed in doses ranging from 187 to 225 mg TID (may not be widely available in this formulation)
- Anticholinergics
 - Relax smooth muscle via anticholinergic effects
 - Dicyclomine 20mg PO QID PRN for 4-6 weeks
 - Hyoscyamine 0.125mg SL QID PRN for 4-6 weeks
- Antispasmodics superior to placebo for reducing abdominal pain, but not as effective as other targeted treatments for IBS

Targeted Pharmacotherapy



- IBS-C

- Lubiprostone
- Linaclotide
- Antidepressants

- IBS-D

- Alosetron
- Rifaximin
- Eluxadoline
- Antidepressants

Lubiprostone (Amitiza[®])



- Activates the chloride channel type 2 (ClC-2) on the apical surface of the intestinal epithelium
 - Chloride and water influx into the intestinal lumen
 - Faster transit through the small and large intestines
- Moderately improves patients perception of constipation symptoms vs. placebo
- Dose: 8 mcg PO BID
- For IBS has only been studied in women (has been studied in men for CIC)
- ADRs
 - Diarrhea
 - Nausea/vomiting
 - First-dose-related dyspnea
- No significant interactions (methadone may reduce efficacy)

Linaclootide (Linzess[®])



- Activates guanylate cyclase-C receptors on the lumen of intestinal epithelium.
 - Increase of cyclic guanosine monophosphate
 - CFTR activation results in secretion of bicarbonate and chloride into the lumen, followed by sodium and water influx
 - Modulation of pain afferent sensors
- Significant effect on IBS symptoms and some effect on pain (stronger evidence than lubiprostone)
- Dose: 290 mcg once daily
- ADRs
 - Diarrhea
 - Flatulence
- No significant drug interactions

Linaclootide vs. Placebo 12 and 26-Week Trials



- 800 patients in the 12-week trial and 804 in the 26-week trial
 - 290mcg daily
 - Treatment success defined as a $\geq 30\%$ decrease in worst abdominal pain + an increase ≥ 1 complete spontaneous bowel movements from baseline for at least 6 / 12 weeks
 - 12 Week: 33.6% vs. 21% ($p < 0.0001$, NNT 8 (5.4-15.5))
 - 26 Week: 33.7% vs. 13.9% ($p < 0.0001$, NNT 5.2 (4-7.3))

Linaclootide vs. Placebo 12 and 26-Week Trials



- ADEs
 - Diarrhea 19.5-19.7% vs 2.5-3.5%
 - Flatulence* 3.7-4.9% vs 1.5-2.2%
 - Abdominal pain* 4.5-5.4% vs 2.5-4.0%
- *significant difference only found in the 12-week trial

Alosetron (Lotronex[®])



- Selective 5-HT₃ antagonist
- Initially withdrawn from the US market due to instances of severe constipation and ischemic colitis
 - Subsequently reintroduced for women suffering with severe diarrhea-predominant IBS that is disabling under a REMS program (Prometheus Prescribing Program)
- Dose:
 - Initial 0.5 mg twice daily for 4 week
 - If inadequate response, may be increased after 4 weeks to 1 mg twice daily.
 - If response is inadequate after 4 weeks of 1 mg twice-daily dosing, discontinue treatment.
- ADRs
 - Constipation, ischemic colitis
- Drug interactions
 - Major metabolite of CYP1A2
 - Use caution with other serotonergic agents

Rifaximin (Xifaxan[®])



- Poorly absorbed antibiotic (inhibits bacterial RNA synthesis by binding to bacterial DNA-dependent RNA polymerase)
 - Proposed mechanism is that eradication of small intestinal bacterial overgrowth is responsible for reduction in IBS symptoms
- Studied in non-constipated IBS
 - Modest, but consistent efficacy in reducing IBS symptoms
- Dose: 550 mg 3 times daily for 14 days; may be retreated up to 2 times with the same dosing regimen if symptoms recur
- ADRs
 - Well tolerated
 - Headache is most common ADR
- Minimal drug interactions, serum concentrations may be increased by p-glycoprotein inhibitors

Target I & II Trials



- Target I&II identical studies, included a total of 1258 patients
- 550mg rifaximin TID x 3 weeks vs. placebo
- Patients evaluated for 3 months, although the primary outcome was determined between weeks 3-6
 - Proportion of patients who reported adequate relief of symptoms in 2 out of 4 weeks.
 - 40.7% with rifaximin vs. 31.7% in placebo P=0.03
 - P=0.001 for relief during the 3 month period for the combined study
- No significant differences in ADRs

Target III Trial



- Unpublished data submitted to the FDA prior to the approval of labeling for IBS
- 2597 patients received open label rifaximin
- 636 patients responded and then met criteria for recurrence 4 weeks after treatment
 - 328 randomized to rifaximin 550mg TID x 2 weeks, then 6 weeks off, followed by a second re-treatment of rifaximin
 - 308 randomized to placebo
 - 32.6% vs 25% of patients responded to retreatment (p =0.0232)
- No serious ADRs

Eluxadoline (Viberzi®)



- Mixed mu-opioid receptor agonist, delta opioid receptor antagonist, and kappa opioid receptor agonist
 - Acts locally on the GI tract to reduce pain and diarrhea in IBS-D
- Dose:
 - 100mg BID, may decrease to 75mg BID if unable to tolerate
 - Start at 75mg BID in patients without a gallbladder
- ADRs
 - Sphincter of Oddi spasm/ biliary duct obstruction
 - Severe constipation
 - Pancreatitis
- Drug interactions
 - OATP1B1 inhibitors: reduce dose to 75mg (i.e. cyclosporine, ritonavir, rifampin)
 - Avoid anticholinergic medications due to potential for severe constipation
 - Avoid alcohol due to potential for pancreatitis

IBS 3001 and 3002 Trials



- 2 phase III trials, compared a total of 2427 patients randomized to eluxadoline 75mg, 100mg, or placebo for 26 weeks (IBS 3001) or 52 weeks (IBS 3002).
- Primary outcome was the number of patients with a decrease in abdominal pain and improvement in stool consistency on the same day for at least 50% of the days during weeks 1-12 and 1-26.
 - Weeks 1-12
 - 100mg 27%, 75mg 26.2%, placebo 16.7% ($p < 0.001$)
 - Weeks 1-26
 - 100mg 31%, 75mg 26.7%, placebo 19.5% ($p < 0.001$)

IBS 3001 and 3002 Trials



- Safety
 - 0.3% of patients developed pancreatitis
 - 0.5% developed sphincter of Oddi spasm
 - Constipation 8% with eluxadoline vs. 2.5% for placebo
 - Nausea and abdominal pain and vomiting more common with eluxadoline

Antidepressants



- May provide relief of abdominal pain, but use can be limited by tolerability
- SSRIs
 - Inhibit reuptake of 5-HT, providing centrally activated analgesic effects
- TCAs
 - Inhibit reuptake of NE and 5-HT, providing centrally activated analgesic effects; also have significant anticholinergic effects
 - Amitriptyline, nortriptyline, and desipramine are the most studied
- Stronger evidence that TCAs are effective compared to SSRIs
 - While antidepressants as a class were combined in the American College of Gastroenterology guidelines, the American Gastroenterological Association recommends TCAs over no treatment, but not SSRIs
- SSRIs may cause significant diarrhea, while TCAs may cause significant constipation
- Low doses should be used (i.e. 10-25mg amitriptyline daily)

Comparison of IBS-C Treatments



Statement	# of Trials	# of Patients	RR (95%CI)	NNT	Strength of Rec.	Evidence Quality
Linacotide is superior to Placebo	3	2,028	0.8 (0.75-0.85)	6(5-8)	Strong	High
Lubiprostone is superior to placebo	2	1,366	0.91 (0.87-0.95)	12.5 (8-25)	Strong	Moderate

RR = relative risk, NNT = number needed to treat, Study outcomes in all trials are either improvement of global IBS symptoms or abdominal pain scores

Comparison of IBS-D Treatments



Statement	# of Trials	# of Patients	RR (95%CI)	NNT	Strength of Rec.	Evidence Quality
Alosetron is effective in female patients with IBS-D	8	4,987	0.79 (0.69-0.90)	8 (5-17)	Weak	Moderate
Rifaximin is effective in reducing IBS symptoms	5	1,805	0.84 (0.78-0.9)	9 (6-12.5)	Weak	Moderate
Eluxadoline is effective in reducing IBS symptoms	2	2427	-	~7.5 to 12.5*	-	-

*estimated from Phase 3 data at 12 weeks for the 100mg dose

Comparison of Other treatments



Statement	# of Trials	# of Patients	RR (95%CI)	NNT	Strength of Rec.	Evidence Quality
Fiber provides overall relief in IBS	14	906	0.86 (0.80-0.94)	10 (6-33)	Weak	Moderate
Probiotics improve IBS symptoms	23	2,575	0.79 (0.7-0.89)	7 (4-12.5)	Weak	Low
Antispasmodics provide short-term symptom relief	23	2,154	0.69 (0.59-0.81)	5 (4-9)	Weak	Low
Antidepressants relieve IBS symptoms	17	1,084	0.67 (0.58-0.77)	4 (3-6)	Weak	High

Question 2



- According to the American College of Gastroenterology, which of the following agents has the strongest level of evidence for the treatment of IBS-C?
 - a. Probiotics
 - b. Antispasmodics
 - c. Polyethylene glycol
 - d. Linaclotide
- Feedback: D. The ACG gave a strong recommendation for the use of linaclotide in IBS-C based on 3 high quality studies in 2,028 patients, with a NNT of 6 (5-8). Although there have been numerous studies of probiotics and antispasmodics, results have been inconsistent, leading to a weak recommendation due to low quality evidence. For polyethylene glycol, there is no evidence that it improves symptoms in patients with IBS.

Question 3



- Which of the following medications is associated with dyspnea that typically occurs with the first dose?
 - a. Alosetron
 - b. Lubiprostone
 - c. Rifaximin
 - d. Eluxadoline
- Feedback: B. Dyspnea, often described as chest tightness, has been reported in up to 3% of patients taking lubiprostone, with onset within the first 30-60 minutes after the first dose, and resolution within a few hours. This has frequently been reported as a recurring symptom with subsequent doses.

Suggested Treatment Algorithm



Diagnosis of IBS

Constipation Predominant

Increase dietary fiber and fluid intake

Add Bulk-forming laxatives, consider antispasmodic agents

Add linaclotide or lubiprostone

Diarrhea Predominant

Consider lactose-free or caffeine-free diet

Add loperamide, consider antispasmodic agents

Add rifaximin or eluxadoline

Consider alosetron if unresponsive

Consider probiotics or antidepressants as adjunctive therapy

Question 4



- GH is a 45yo M with a history of type 2 diabetes, chronic pancreatitis, and diarrhea predominant IBS, who presents to clinic with symptoms of abdominal discomfort associated with more frequent, loose stool, refractory to increased dietary fiber and loperamide. Which of the following is the best agent to initiate in patient GH?
 - a. Alosetron
 - b. Eluxadoline
 - c. Rifaximin
 - d. All of the above are appropriate
- Feedback: While all 3 of these medications are used for IBS-D, alosetron has only been studied in female patients and eluxadoline is contraindicated in patients with a history of pancreatitis. Rifaximin is the only appropriate choice for initiating in patient GH. Another consideration not listed would be in starting a tricyclic antidepressant in this patient for the treatment of abdominal discomfort

Take Home Points



- IBS is a common condition that can cause significant discomfort for patients beyond merely changes in stool frequency
- Dietary modifications and other non-pharmacologic therapy can help with some IBS symptoms
- New targeted therapies can offer assistance to patients that are not experiencing relief from non-pharmacologic and symptomatic therapies
- Although new treatments exist, not every patient will respond to any one treatment

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