GI ReConnect

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GI Health Foundation

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IBS-D Pharmacotherapy

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Faculty Disclosure

Lucinda A. Harris, MS, MD

- Consultant: AbbVie (formerly Allergan), Alynam, Common Wealth Laboratories, Ironwood, The Rome Foundation, Salix, Takeda
- Research: Alkos
- Member: The Rome Foundation

Current FDA-Approved Pharmacotherapy

- Alosetron
- Eluxadoline
- Rifaximin

Alosetron

- 5HT-3 Serotonin Antagonist
- 0.5 -1.0 mg bid
- Approved for women only with severe IBS-D
- NNT[1] = 8
- Side effects – Ischemic colitis and severe constipation
- Taken off market in 2000, came back 2002 REMS program
- Use with caution with ketoconazole
- Contra-indicated with fluvoxamine

1. Ford A et al. *Am J Gastroenterol*. *2014;* 109: Suppl 1: S2-S26.

Alosetron: Therapeutic Gain for IBS-D

Study	N	% Female	Response Alosetron %	Response Placebo %	Therapeutic Gain %
Camilleri[1]	370	53	60	33	27
Camilleri[2]	647	100	41	29	12
Camilleri[3]	626	100	43	26	17
Lembo[4]	801	100	73	57	16
Jones[5*]	623	100	58	48	10

*Comparison mebeverine† instead of placebo
† Mebeverine is not available in the USA

1. Camilleri M et al. *Aliment Pharmacol Ther*. 1999; 13: 1149-1159; 2. Camilleri M et al. *Lancet*. 2000; 355: 1035-1040;
3. Camilleri M et al. *Arch Intern Med*. 2001; 161: 1733-1740; 4. Lembo T et al. *Am J Gastroenterol*. 2001; 96: 2662-2670;
5. Jones R et al. *Aliment Pharmacol Ther*. 1999; 13: 1419-1427.

New ACG IBS Consensus Guidelines:
Scope & Methodology[1]

- 25 Clinical Statements
- Individualized literature search
- Trained GRADE methodologists analyzed the data
- Modified Delphi approach to achieve consensus
- GRADE guidelines where applicable

Summary of Quality of Evidence

Recommendation	Quality of Evidence
Strong: The strength of recommendation is given as strong if most patients should receive the recommended course of action	High–the estimate of effect is unlikely to change with new data
Conditional: The strength of recommendation is given as conditional if many patients should have this recommended course of action, but different choices may be appropriate for some patients	Moderate; low; very low–estimate of effect is very uncertain

1. Lacy BE et al. *Am J Gastroenterol*. 2021; 116: 17-44.

AGA Technical Review of Pharmacotherapy for IBS[1] (2021)

- Methodology
  - Focused clinical questions reviewing & rating quality of evidence based on GRADE framework
  - Identified PICO* questions
  - For IBS-D – Alosetron, Rifaximin, Tricylic Antidepressants and Antispasmodics,Loperamide and Eluxadoline
  - New review pending

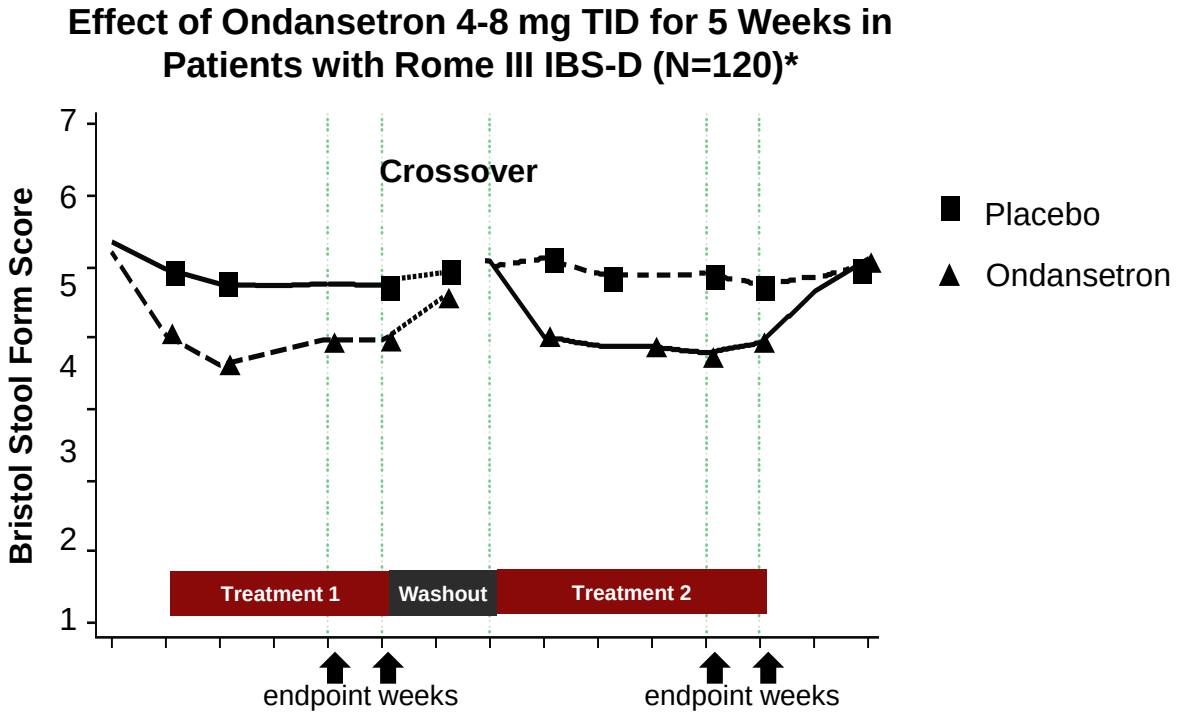
* PICO-Population, Intervention, Comparator (placebo or control) & Outcome (Benefits & Harms)

1. Chang L et al. *Gastroenterol*. 2021 (in press).

Alosetron: ACG Consensus Guideline Recommendation vs. AGA Guidelines

- **Recommend Alosetron be used to relieve global IBS-D symptoms in women with severe symptoms of IBS who have failed conventional therapy. *Conditional recommendation, low quality of evidence***
- **AGA – *Conditional recommendation, overall quality of evidence across all outcomes was moderate***
- Initial safety concerns tempered by follow-up data - low, stable adjudicated incidence rates of ischemic colitis and reduced complicated constipation (1.03 cases and 0.25 cases/1,000 patient-years of exposure, respectively)

Ondansetron for IBS-D (Not ACG-graded)



*Randomized, double-blind, dose-titration study. Primary endpoint was average stool consistency in last 2 weeks of treatment. Improvements in urgency, frequency, bloating but NOT pain.

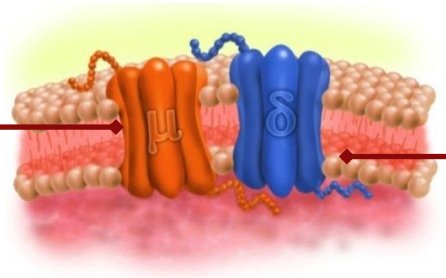
Garsed K et al. *Gut*. 2014; 63: 1617-1625.

Eluxadoline: Pharmacotherapy

- Mixed mu (μ) and kappa (κ) opioid receptor agonist / delta (δ) opioid receptor antagonist
- Low systemic absorption and bioavailability
  - Low potential for drug-drug interactions
- Animal studies suggest eluxadoline should improve the diarrheal symptoms of IBS-D with limited constipation and durable analgesia

μ opioid receptor

Activation reduces pain, gastric propulsion



δ opioid receptor

Inhibition restores G-protein signalling; reduces μ agonist-related desensitization

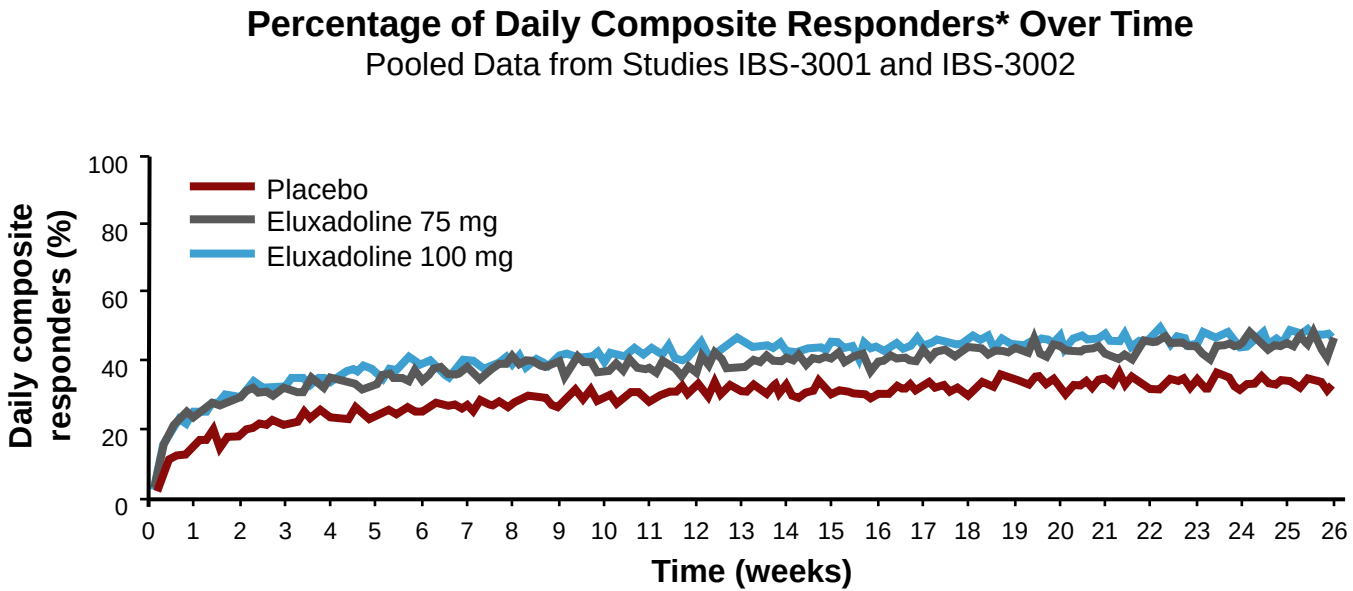
Lembo A, Lacy BE, et al. *N Engl J Med.* 2016: 374: 242–253.

Safety of Eluxadoline in Patients With IBS-Diarrhea

- 2,814 IBS-D patients (Rome III criteria)
- Placebo vs. eluxadoline (75 or 100 mg b.i.d.)
- 1 Phase 2 study (12 weeks) and 2 Phase 3 studies (26 and 52 weeks)
- Most frequent AEs:
  - Constipation (2.5% vs. 7.4% vs. 8.1%)
  - Nausea (5.0 vs. 8.1 vs. 7.1%)
- 10 Patients had Sphincter of Oddi Spasm (0.5%); all in patients with prior cholecystectomy
- 8 Patients had pancreatitis (0.3%) – drug contra-indicated in patients with history of alcohol abuse or addiction, or who drink > 4 alcoholic drinks per day

Cash BD et al. *Am J Gastroenterol*. 2017: 112: 365-374.

Eluxadoline in IBS-D: Percentage of Daily Composite Responders Over Time



*Composite responders met criteria of daily pain responder and daily stool consistency responder on the same day, with ≥50% of days demonstrating a response. Daily pain responder defined as ≥30% improvement in WAP scores by in the past 24 h compared with average baseline pain. Daily stool consistency responder defined as BSS score <5 (or in absence of BM, if accompanied by ≥30% improvement in WAP compared with average baseline pain).

Lembo AJ et al. *N Engl J Med*. 2016; 374: 242-253.

Eluxadoline: ACG Consensus Guideline Recommendation vs. AGA

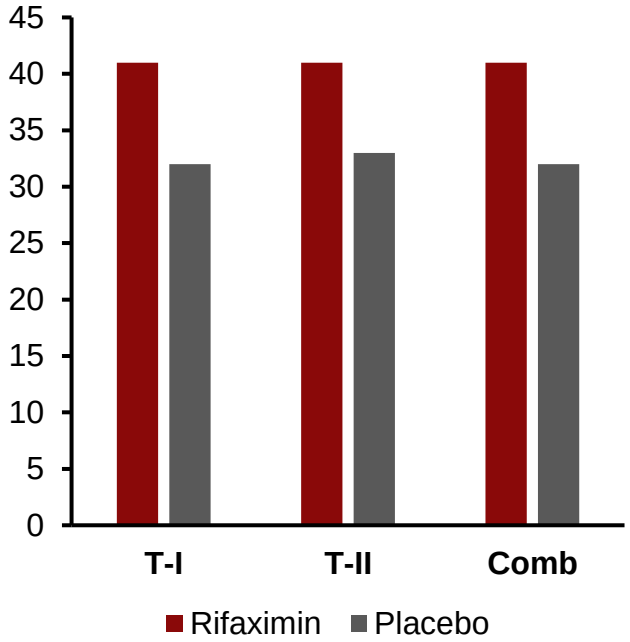
- **ACG – Suggest Mixed Opioid Antagonists be used to treat global IBS-D symptoms. *Conditional recommendation, moderate quality of evidence***
- **AGA – Suggests using eluxadoline over no treatment. *Conditional recommendation, moderate quality of evidence***
- 75 or 100 mg bid for both men and women – lower dose for those with hepatic impairment or are receiving concomitant OATP1B1 inhibitors
- Composite endpoint of improving pain and daily stool consistency

Rifaximin

- Minimally absorbed broad-spectrum antibiotic that acts locally in the GI tract and inhibits bacterial transcription and ribonucleic acid synthesis
- Studies suggest that mechanism of action is an alteration in the microbiome – suggested by breath testing
- Approved 550mg tid for 2 weeks for both men and women for up to 3 courses
- NNT = 9

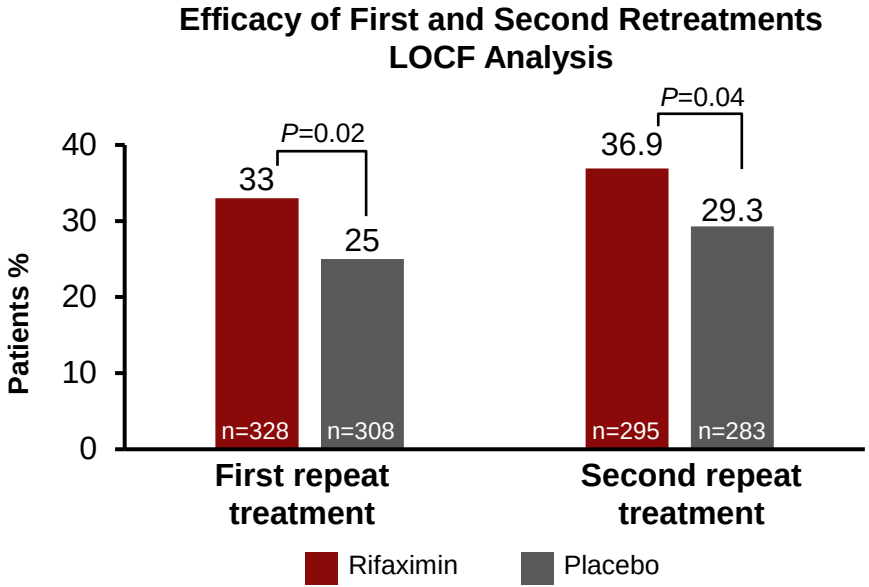
Rifaximin Trials: Global Relief of IBS Without Constipation

- 2 Phase 3 randomized controlled trials; N=1260 patients
- Rifaximin 550 mg TID x 2 weeks; patients followed additional 10 weeks
- 40.7% vs. 31.7% with adequate relief of global symptoms (*P*<0.001)



T-I, TARGET 1 trial; T-II, TARGET 2 trial; Comb, Combination of both trials.
*Rifaximin is FDA-approved for non-constipation IBS.
Pimentel M et al. *N Engl J Med.* 2011; 364: 22-32.

TARGET 3:
Efficacy of First and Second Retreatments



Urgency and bloating improved significantly with both repeat treatments

Abdominal pain and stool consistency improved significantly with first retreatment

LOCF, last observation carried forward.
Responder defined as subjects responding to IBS-related Abdominal Pain and Stool Consistency for ≥2 of 4 weeks.
Recurrence defined as a loss of response for ≥3 of 4 weeks.
Chey WD et al. *Effects of Rifaximin on Urgency, Bloating, and Abdominal Pain in Patients with IBS-D: A Randomized, Controlled, Repeat Treatment Study*. Presented at DDW, May 16-19, 2015; Washington, D.C. [Abstract No. 313].

Rifaximin ACG Guideline Recommendation vs. AGA Technical Review

- **ACG – Recommend use of rifaximin to treat global IBS-D symptoms. *Strong recommendation, moderate level of evidence***
- **AGA – Suggests using rifaximin over no treatment. *Conditional recommendation, moderate level of evidence***
  - AGA – If pt has initial response and recurrent sx, AGA recommends retreatment. *Conditional recommendation, moderate level of evidence*

Other Pharmacotherapy for IBS-D

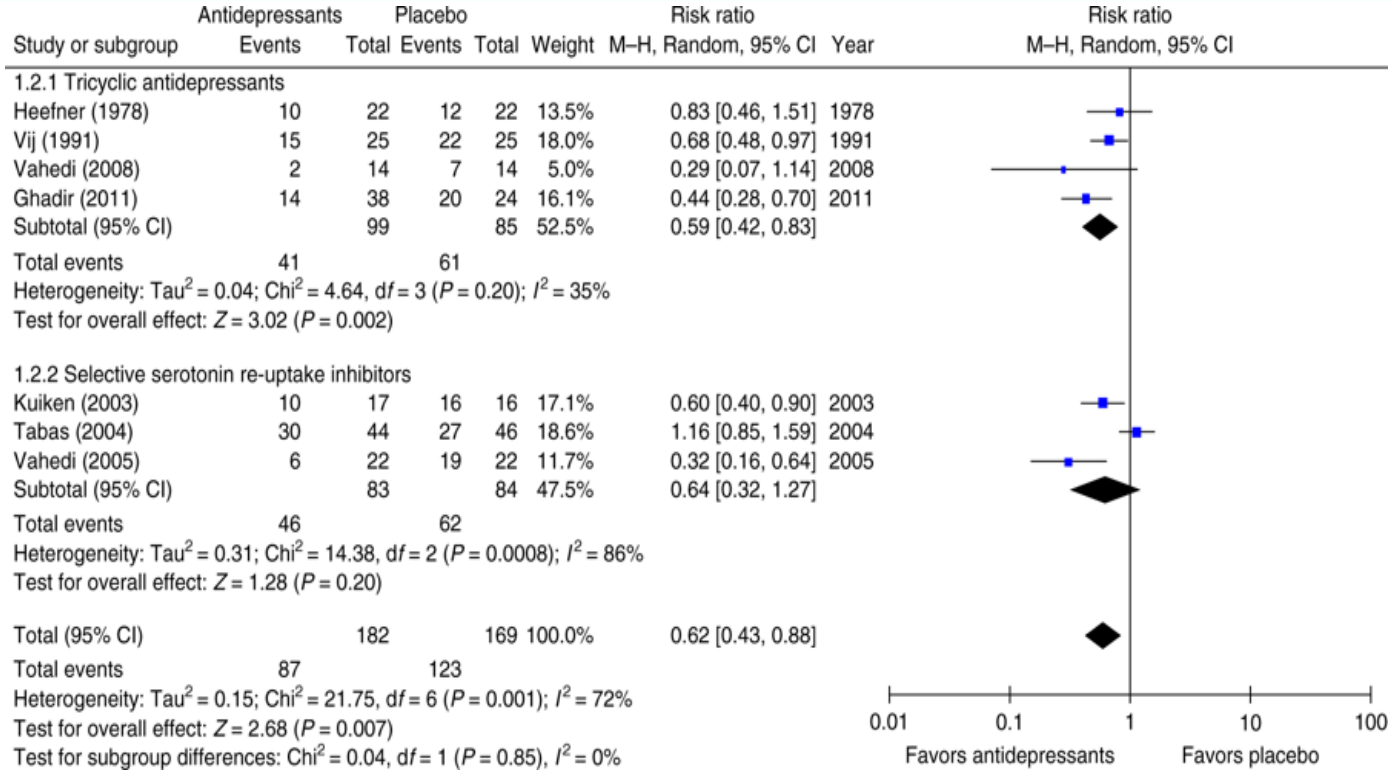
- Tricyclic Antidepressants – (amitriptyline, imipramine, desipramine, nortriptyline)
- Antispasmodics (hyoscyamine, dicyclomine, peppermint oil)
- Bile acid sequestrants (cholestyramine, colsevelam, colestipol)
- Probiotics (Bifidis bacteria -35624,)
- Loperamide
- Medical foods (peppermint oil, bovine immunoglobulin/ protein isolate)
- Glutamine

Tricyclic Antidepressants – ACG Consensus Guidelines vs AGA Technical Review

- **Recommend that TCAs be used to treat global symptoms of IBS. *Strong recommendation, moderate quality of evidence***
  - Start low and go slow
  - Can improve visceral and central pain
  - Can help pt with co-morbid conditions
  - Avoid in pts with QT prolongation
  - Secondary amines have less antihistamine & anti-cholinergic effects, less likely to cause sedation and constipation
- **AGA – recommends treatment. *Conditional recommendation, low quality of evidence***

Name	Class	Dose (mg)	Side effects
Amitriptyline	Tertiary Amine	50-100	Dry mouth, urinary retention, sedation, wt gain, cardiac arrythmias, sexual dysfunction, constipation, blurry vison
Imipramine	Tertiary Amine	50-100	“
Desipramine	Secondary Amine	25-100	Dry mouth, urinary retention, cardiac arrythmias, wt gain, dizziness, nausea, HA
Nortriptyline	Secondary Amine	25-75	“

Forest Plot of Randomized Controlled Trials of Antidepressants vs. Placebo – Effect on Abdominal Pain in IBS



Ford, Lacy, Harris, Quigley, Moayyedi. *Am J Gastroenterol*. 2018; epub ahead of print.

Antispasmodics – ACG Consensus Guideline Recommendation vs AGA TR

- **Recommend against the use of antispasmodics currently available in the US to treat global IBS symptoms – *Conditional recommendation, low quality of evidence***
- **AGA – suggests use of antispasmodics – *Conditional recommendation, low quality of evidence***
- Hyoscyamine and Dicyclomine – medications in the USA
- Published studies – methodologically limited b/o small sample size, lack of standardized enrollment criteria, different trial designs, and different endpoints
- Side effects are common – especially the elderly.
- Some antispasmodics available outside USA may be of greater efficacy

Bile Acid Sequestrants – ACG IBS Consensus Guidelines Recommendation

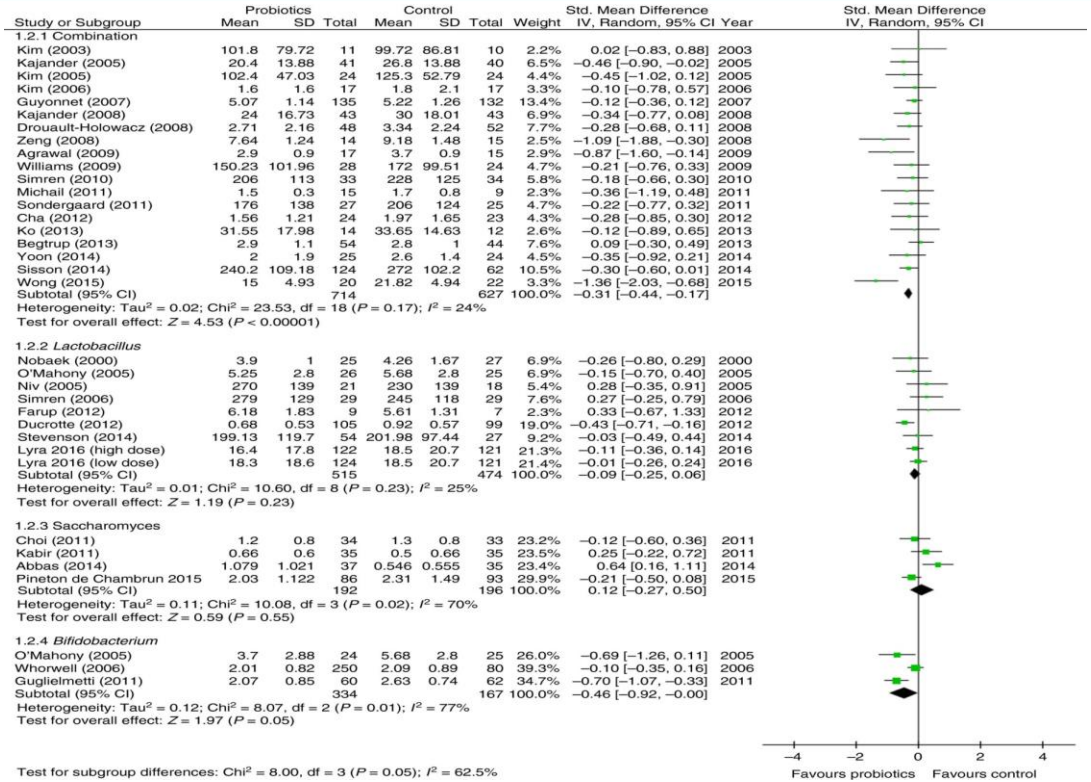
- **Suggest <u>against</u> the use of bile acid sequestrants to treat global IBS-D symptoms.** ***Conditional recommendation, very low level of evidence***
- 3 mechanisms for increased bile acids in IBS:
  1. Iatrogenic loss of the distal small bowel reducing the absorbing capacity
  2. Cholecystectomy leading to a change in timing of bile delivery to the small intestine
  3. Idiopathic form possibly related to the differential potential for reabsorption of bile acids in given individuals has been identified
- Bile acid sequestrants have been studied in small populations, larger studies are needed

Probiotics – ACG Consensus Guideline Recommendation

- **Suggest <u>against</u> probiotics for the treatment of global IBS symptoms – *Conditional recommendation, very low level of evidence***
  - Purported benefits:
    1. Competitive inhibition
    2. Barrier protection
    3. Immune effects
    4. Anti-inflammatory effects
    5. Ability to alter pH & physiology
    6. Nutrition to enterocytes
    7. Production of SCFAs, etc.
- **IMPORTANT AREA OF RESEARCH GIVEN INTEREST IN MICROBIOME**

Forest Plot of Randomized Controlled Trials of Probiotics vs Placebo in IBS:

Effect on Global Symptom or Abdominal Pain Scores



Ford A, Harris L, et al. *APT*. 2018; 48: 1044-1060.

Loperamide – ACG Guidelines vs. AGA Technical Review

- **ACG[1] – 2018 – suggested <u>against</u> the use of loperamide, *recommendations strong, quality of evidence low***
- **AGA – suggested using loperamide, *conditional recommendation, very low quality of evidence***
- 2 trials[2,3] involving 42 pts (one IBS-M, one IBS-D), There was a lack of beneficial effect on global improvement of symptoms of IBS and urgency. There was significant improvement in abdominal pain and stool consistency

1. Ford A et al. *Am J Gastroenterol*. 2018: 113: 1-18; 2. Hovdenak N et al. *Scand J Gastroenterol*. 1987: 130: 81-84;
3. Lavo B et al. *Scand J Gastroenterol*. 1997: 130: 77-80.

Peppermint Oil – ACG IBS Consensus Guidelines Recommendation

- **Suggest the use of peppermint oil to provide relief of global IBS symptoms – *Conditional recommendation, low quality of evidence***
  - Therapeutic effect - L-menthol's blockade of calcium channels and attendant smooth muscle relaxation
- **Other effects:**
  - modulation of transient receptor potential voltage channels decreasing visceral sensation
  - direct antimicrobial and anti-inflammatory effects
- **NNT[1]** – of 3 for overall IBS symptoms and 4 for abdominal pain from recent meta-analysis
  - Only small number of commercially available preparations were well studied

1. Alammar N et al. *BMC Compliment Altern Med*. 2019; 19:21.

Serum-derived Bovine Immunoglobulin/ Protein Isolate (Not ACG-graded)

- Mechanism – providing nutritional support for epithelial barrier function and maintaining immune balance in the GI tract
- **Pilot study**[1] – DBRPC 6-week study in patients with IBS-D (*n* = 66), SBI 10 g/day and 5 g/day significantly reduced # of days with any symptom between weeks 2 and 6 compared with baseline (assumed that 3 weeks' treatment would be needed before benefits would be observed)
- Benefits greater for 10 g/day dose and similar safety profile compared to placebo
- Case series[2] report suggest it improves abdominal pain & bowel movements for 17-32 weeks
- Larger and longer-term clinical studies are required to assess the efficacy and safety of SBI in IBS-D

1. Wilson M et al. *Clin Med Insights Gastroenterol*. 2012: 6: 49–60; 2. Good A et al. *World J Gastroenterol*. 2015; 21: 3361–3366.

Glutamine – (Not ACG-graded) for PI-IBS

- RDBPC trial[1] of glutamine (5 g/t.i.d.) vs. placebo for 8 weeks. (N=104, 70% F)
- **Primary end point** – reduction of ≥50 points on the IBS Symptom Severity Score (IBS-SS).
  - Met in 43 (79.6%) G vs 3 (5.8%) P
- **Secondary endpoints**
  1. Raw IBS-SS scores – IBS-SS at 8 weeks (301 vs. 181, $p<0.0001$)
  2. Change in daily BMs # – Daily BM frequency (5.4 vs 2.9±1.0, $p<0.0001$),
  3. Stool form(Bristol Stool Scale); Bristol Stool Scale (6.5 vs 3.9, $p<0.0001$); and
  4. Intestinal permeability (lactulose: mannitol ratio) (0.11 vs 0.05; $p> 0.0001$)

1. Zhou Q-Q et al. *Gut*. 2018; 68: 996-1002.