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# IBS – Therapeutics Bible class

Benjamin Misselwitz

6th of October 2021

# Guidelines 2021

## British Society of Gastroenterology guidelines on the management of irritable bowel syndrome

Dipesh H Vasant [1,2], Peter A Paine,[2,3] Christopher J Black [4,5], Lesley A Houghton [5,6], Hazel A Everitt,[7] Maura Corsetti,[8] Anurag Agrawal,[9] Imran Aziz [10,11], Adam D Farmer,[12,13] Maria P Eugenicos,[14] Rona Moss-Morris,[15] Yan Yiannakou,[16] Alexander C Ford [4,5]

Vasant DH, *et al*. *Gut* 2021;**70**:1214–1240. doi:10.1136/gutjnl-2021-324598

## ACG Clinical Guideline: Management of Irritable Bowel Syndrome

Brian E. Lacy, PhD, MD, FACG[1], Mark Pimentel, MD, FACG[2], Darren M. Brenner, MD, FACG[3], William D. Chey, MD, FACG[4], Laurie A. Keefer, PhD[5], Millie D. Long, MDMPH, FACG (GRADE Methodologist)[6] and Baha Moshiree, MD, MSc, FACG[7]

*Am J Gastroenterol 2021;116:17–44. https://doi.org/10.14309/ajg.0000000000001036; published online December 14, 2020*

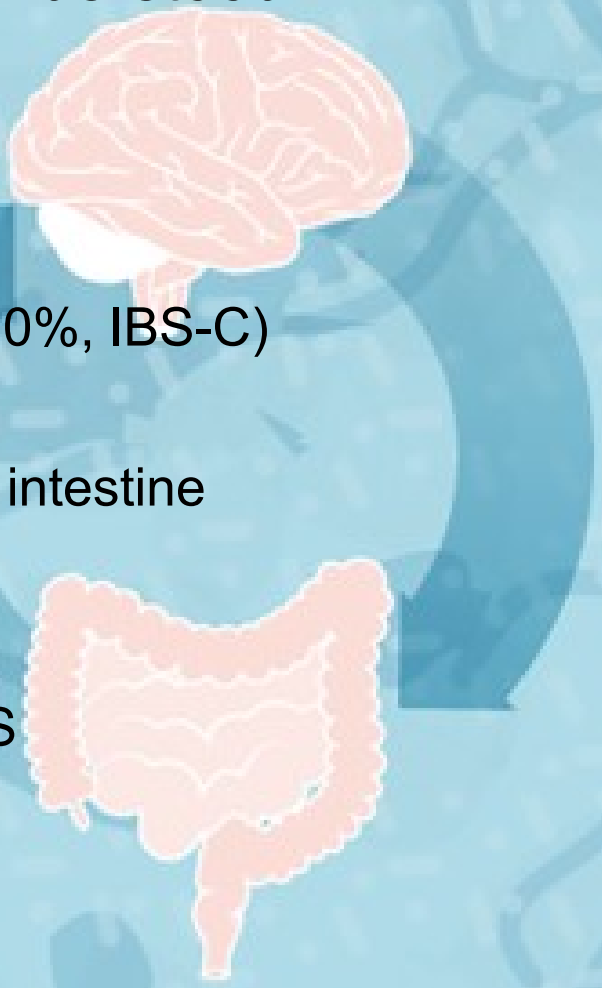
## Unpublished 2021 S3 Guidelines «Reizdarmsyndrom»

https://www.awmf.org/uploads/tx_szleitlinien/021-016l_S3_Definition-Pathophysiologie-Diagnostik-Therapie-Reizdarmsyndroms_2021-07.pdf

# IBS - Pathophysiology

The pathophysiology of IBS is incompletely understood
→ Disorder of gut – brain interaction

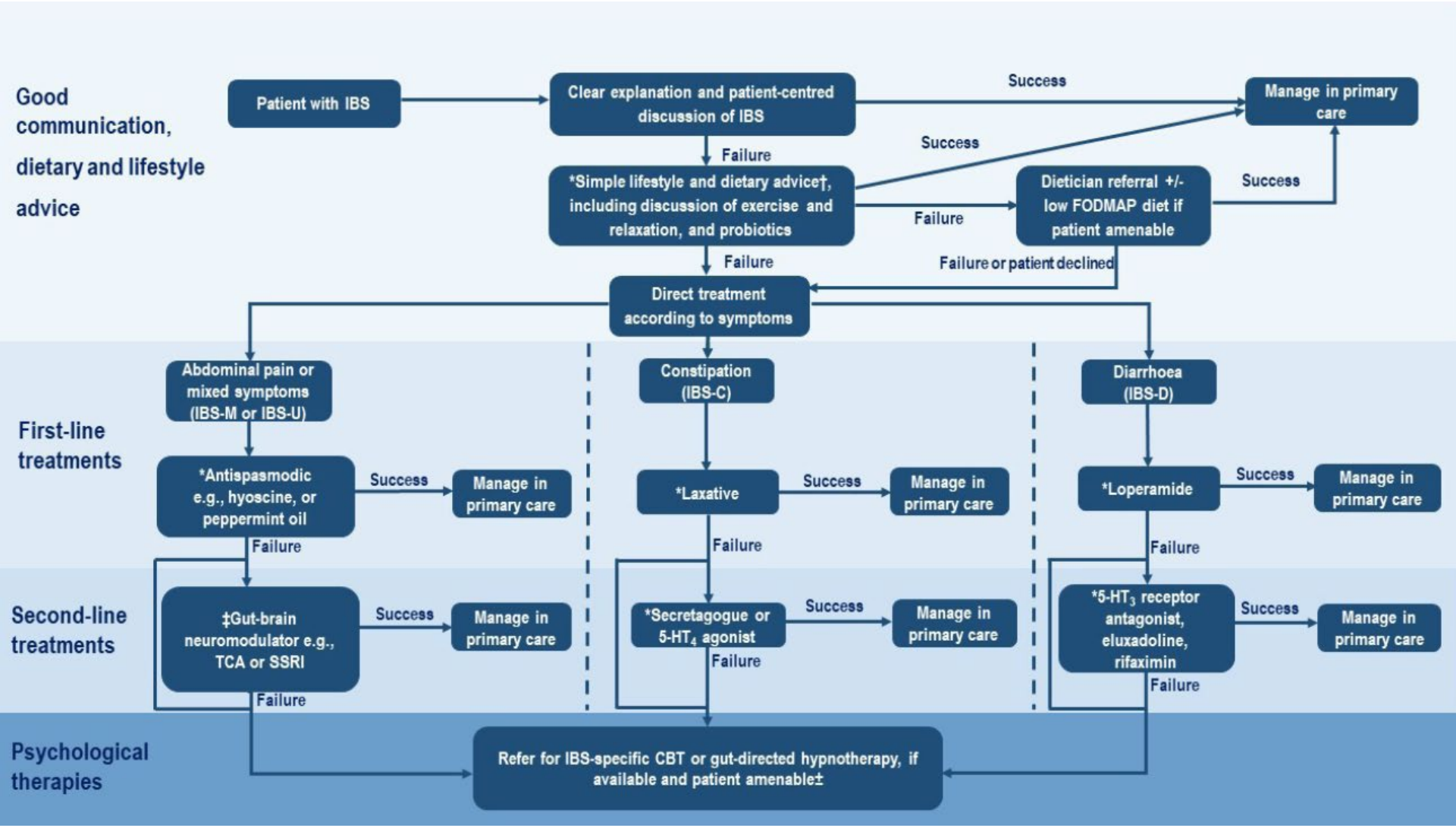
- Altered central pain processing, hypervigilance
  symptom related anxiety
- Visceral hypersensitivity/ visceral hyposensitivity (20%, IBS-C)
- Subtle physiological alterations
  - higher number of mast cells in colon and small intestine
  - lower expression of tight junction proteins
  - lower IL-10 expression
- Bacterial, viral or parasitic infections can trigger IBS
- Some genetic changes have been identified



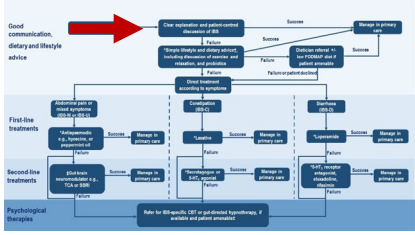
**In 2021, no „positive“ test for IBS exists.**

Vasant et al., Gut 2021; 70:1214

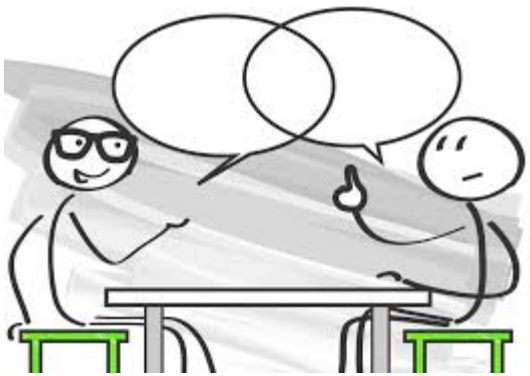
# IBS - Treatment algorithm



# It matters how we talk to our patients



- «Establishing an **effective doctor-patient relationship** and a shared understanding is key to the management of IBS.»
- «Patients with IBS would like increased **empathy**, **support** and **information** from clinicians about the nature of the condition, diagnosis and symptom management options.»
- «Empathic listening» to optimise the interaction
  → 2 minutes of active listening at the beginning of a consultation…



**Personal experience (BM)**
**Consultations with IBS patients are:**

- Time consuming
- Physically and psychologically very demanding
- The most difficult task in gastroenterology

# How to talk to the patient: Make a positive diagnosis

**The diagnosis of IBS is secure if**
- Patient has typical symptoms (Rome III, IV)
- No alarm symptoms
- Presents with additional symptoms (bloating, headache, back pain…)
- No abnormal findings during work-up
- Test of time: fluctuating but overall identical symptoms for >2…5…20 years

**A positive diagnosis of IBS**:
- Improves symptoms
- Reduces the number of additional investigations (by 2-fold)
- Saves costs (by $400 per patient)

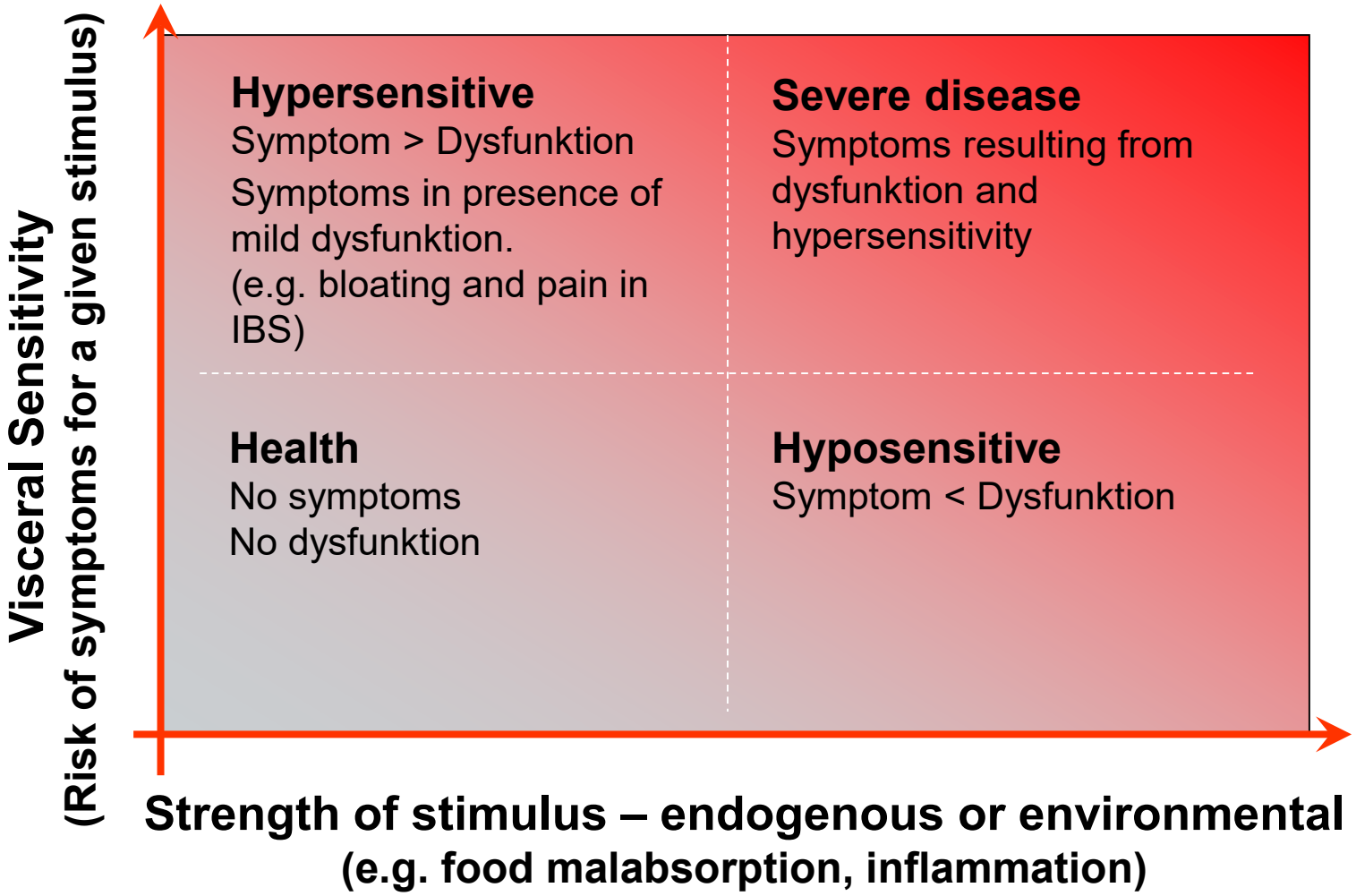
**Clear positive diagnostic language**:
- *"he/ she is suffering from"*
- *"he/ she is diagnosed with…"*
- *"I have diagnosed him/ her with…*

**Qualifying exclusion language**:
- *"may be suffering from…"*
- *"it's possible that…"*
- *"fits the picture of…"*

→ Qualifying language in 63% of functional vs. 13% of organic GI disorders
→ More diagnostic investigations for functional disorders

Spiegel et al., Am J Gastroenterol. 2010; 105:848
Linedale et al., Clin Gastroenterol Hepatol 2016; 14:1735

# Make the patient aware of the diagnosis + Explain disease mechanisms

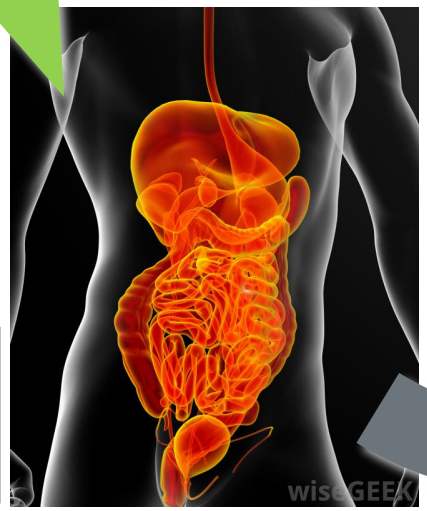



Based on: Fox & Schwizer Gut 2008:57:435-9

# Symptom Generation in Functional GI Disease: a Model


Intestinal symptoms increase **Stress**

The brain modulates and filters sensations from the gut



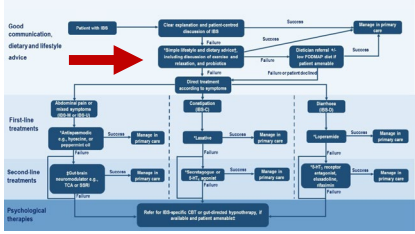
Symptoms are generated in the GI tract by the enteric nerve system

**Stress** impacts on **bowel function**

Explanation of these mechanisms frequently improves symptoms.

Gibson P. J Gastroenterol Hepatol. 2011; 26 S3:128

# Exercise



*«All patients with IBS should be advised to take regular exercise»*
recommendation: strong, quality of evidence: weak.

Moderate to vigorous physical activity for 20-60min 3-5 days per week

| | Exercise group | Control group |
|---|---|---|
| | N=37 | N=38 |
| Improvement in IBS-SSS | -51 points | -5 points; p=0.003 |
| Clinical improvement | 43% | 26%; p=0.07 |
| Worsening of IBS symptoms | 8% | 23% |

Choose your favorite exercise…

Johannesson et al. Am J Gastroenterol. 2011; 106:915

# Nutritional interventions

**Traditional dietary advice**: No formal dietetician input necessary

- Adopting «healthy eating patterns»
  - Regular meals
  - Maintaining adequate nutrition
  - Exclude gas producing foods (beans, cabbage, onions)
  - Limiting alcohol and caffeine intake
  - Reducing consumption of fatty and spicy foods.

- Adjusting fibre intake
  - Soluble fibers: RR of IBS symptoms persisting=0.87; 95% CI 0.80 to 0.94

# Ajustment of fiber intake

Natural fibers – start low (3-4 g/d)

… increase to recommended 20-30 g/d

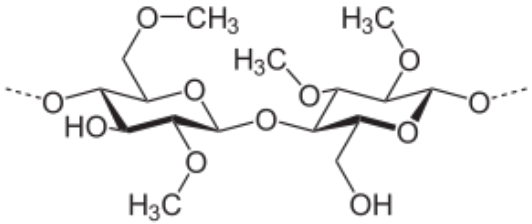
- Natural fibers
  - 3.5g in one apple with skin
  - 4.6g in one pear with skin
  - 11.9g per 11 dried prune
  - 5g in one cup of broccoli with stalk
  - 0.5g per slice of white bread
  - 1.7g per slice of whole-wheat bread
- Main side effect: bloating

Kim et al., Gastroenterology 2000; 118:1235

# Natural/ synthetic fiber supplementation

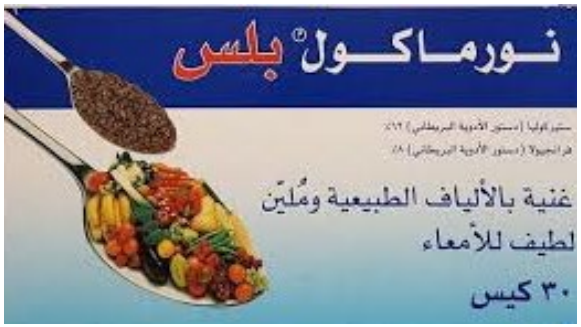
**Psyllium**

- Psyllium seed (Metamucil®)
  *Indian flea seed husks*
- Methylcellulose
- Wheat dextrin
- Sterculia gum (Normacol®)
  *bark of Indian rubber tree*

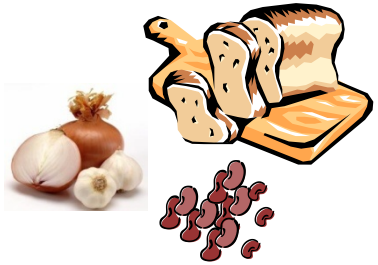


**Methylcellulose**

Main side effect: bloating/ distension
→ Compliance ~50%
→ Dose titration (until stool consistency changes)
→ “regular defecation” is typically achieved (but not necessarily freedom from pain)

**F***ermentable*



**O**ligosaccharides → **Fructo-oligosaccharide** (Fructans)
**Galacto-oligosaccharide** (GOS)

**D**isaccharides → **Laktose** (Laktulose)

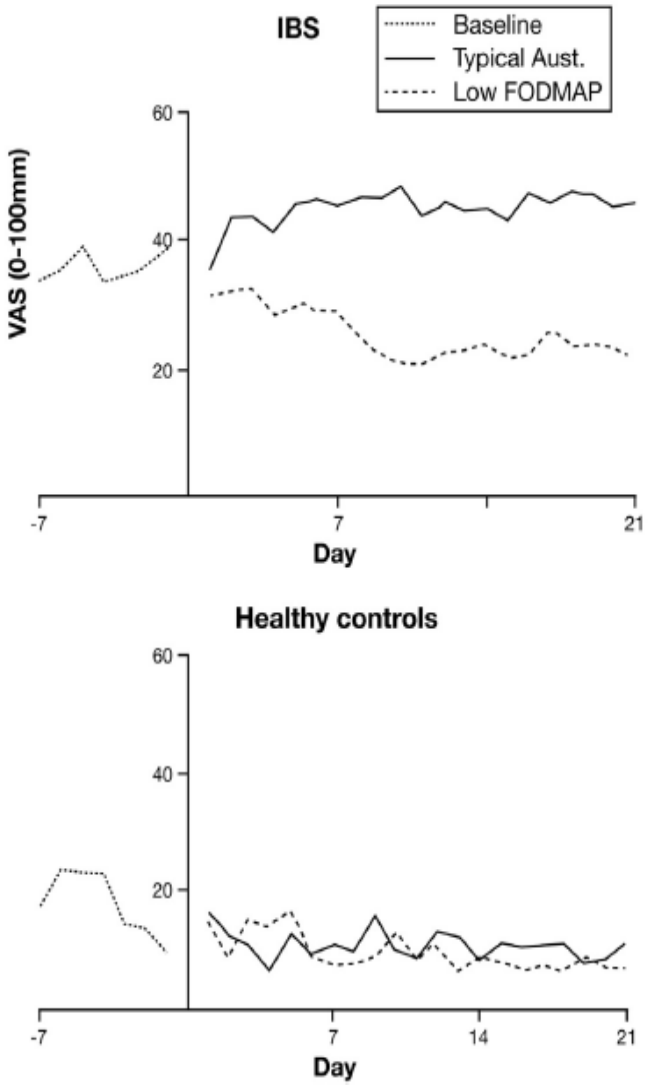
**M**onosaccharides

→ **Fruktose**

***A**nd*

**P**olyol**s** → **Sorbitol, Mannitol**

# A low FODMAPs diet can reduce IBS symptoms




- Randomized controlled, single-blind, crossover
- 30 patients with IBS + 8 HV
- FODMAPs content:
  - *Low FODMAP: 3 g/Tag*
  - *Typical Australian diet: 24 g/Tag*

- Pain in IBS patients has significantly improved under low FODMAPs diet
- No effect in HV

Halmos et al., Gastroenterol 2014; 146: 67

# Low FODMAPs diet reduces IBS symptoms

50-70% free of symptoms in some studies

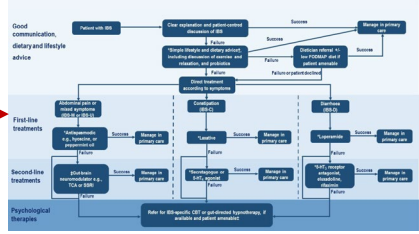
**In controlled trials against all other interventions:**
RR 0.71; 95% CI 0.61 to 0.83

**Compared to traditional dietary advice** from NICE and the BDA
RR 0.82; 95% CI 0.67 to 1.01
lower heterogeneity, lower effect size

**General problems with the FODMAPs evidence:**
- Difficulties in blinding
- High heterogeneity of studies
- Trials focus on 4-6 week induction period
  subsequent re-introduction and personalization period is less studied

**Gluten free diet in IBS?**
Not supported by strong evidence (RR 0.42; 95% CI 0.11 to 1.55)
Popular among patients → further studies are warrented

# First line drugs



**Loperamid** IBS-D
Improves stool frequency
no effect on global symptoms (RR 0.44; 95% CI 0.14 to 1.42)
Side effects: constipation, nausea, bloating

**PEG-based laxatives** IBS-C
Week evidence
Side effect: abdominal pain

**Peppermint oil**
Improves global symptoms or abdominal pain (RR 0.58; 95% CI 0.34 to 0.98)
Side effect: reflux

**Antispasmodics**
Improves IBS symptoms: RR 0.65; 95% CI 0.56 to 0.76)
hyoscine butylbromide, (butylscopolamine)
Side effects: dry mouth, visual disturbance and dizziness

# Second line drugs: gut – brain neuromodulators

**Tricyclic antidepressents (TCA)**
12 RCTs of TCAs, recruiting 787 patients
Improve global symptoms or abdominal pain: RR 0.65; 95% CI 0.55 to 0.77
Side effects: drowsiness and dry mouth, cardiac arrhythmia
→ e.g. Amitriptylin 10 mg → increase in 10 mg increments until 30-50 mg
(anti-depressent dosage: 75…100…150mg/d)
→ Trimipramin drops (1 mg = 1 drop)
10 drops … 30-50 drops per day
anti-depressent dosage: 50-150mg, max: 300mg/d

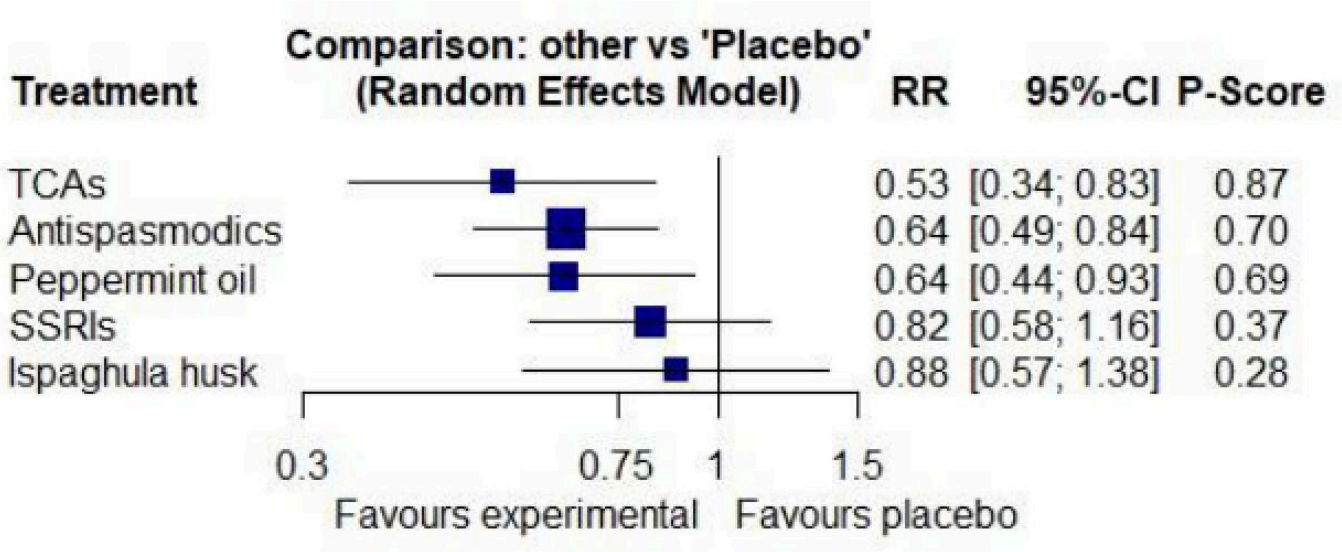
**Selective serotonine reuptake inhibitors (SSRI)**
e.g., with comorbid anxiety
Improve global symptoms or abdominal pain (RR 0.68; 95% CI 0.51 to 0.91)

Alternatives: calcium channel α2δ ligands (pregabaline), SSNRI (duloxetine)

*Clear communication: «SSRI/ TCA are at low doses for their pain modulatory properties and peripheral effects on gastrointestinal function, rather than at a dose that is used to treat common mental disorders»*

# Network meta-analysis
# Treatment of abdominal pain in IBS

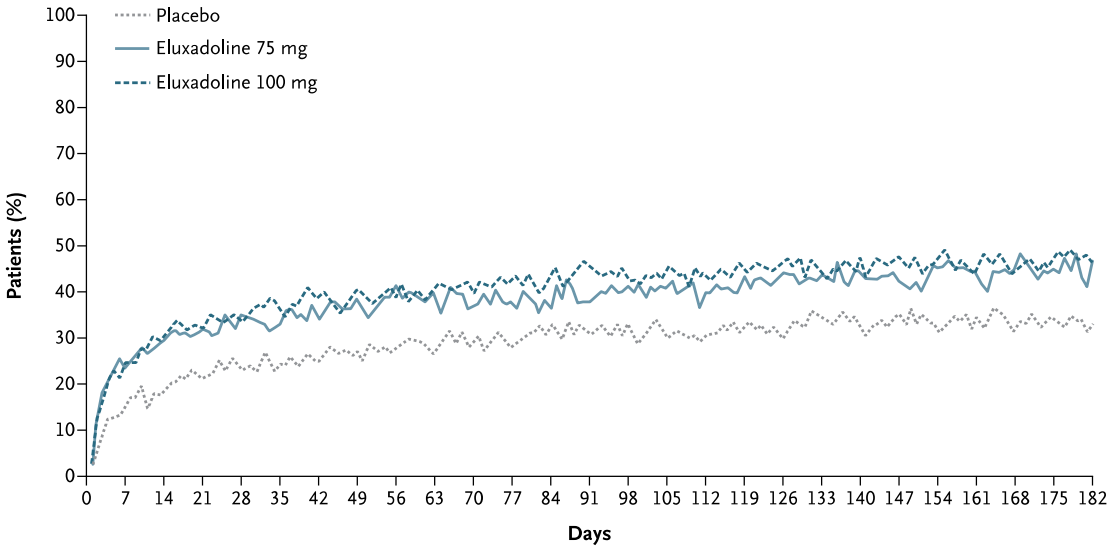
**Network meta-analysis: treatment of abdominal pain**



# Second line drugs for IBS-D: Eluxadoline (Truberzi®)

Mechanism: μ- and κ-opioid receptor agonist and δ-opioid receptor antagonist

Endpoint: decrease in abdominal pain and improvement in stool consistency on the same day for at least 50% of days




N=2427

Response rates:

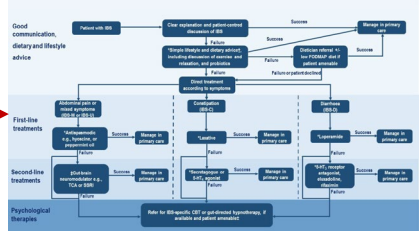
| | |
|---|---|
| Eluxadoline 2x75 mg: | 30.4% |
| Eluxadoline 2x100 mg: | 32.7% |
| Placebo: | 20.2% |

→ 0.3% pancreatitis, Sphincter Oddi Spasm

4 RCTs with 3122 patients:
→ abdominal pain RR 0.89; 95% CI 0.84 to 0.94
→ stool consistency RR 0.87; 95% CI 0.83 to 0.91

**Modest improvement in symptoms and diarrhea in IBS-C**
**Cave: No comparison to laxatives**

Lembo et al., NEJM 2016;374:242



# Second line drugs IBS-D
# 5-Hydroxytryptamine 3 receptor antagonists

**Alosetron:** ischemic colitis
**Ramosetron:** only available in Asia

**Ondansetron** Zofran®

→ Start Ondansetron 4 mg 1x/d
→ Increase to 4 mg 6x/d
→ Constipation: decrease to last tolerated dose

Improves urgency, bloating and stool consistency, but not abdominal pain
Side effects: constipation, nausea, bloating

Garsed et al., Gut 2014; 63:1617

# Second line drugs IBS-D: Rifaximin

**Treatment trials (TARGET-1, 2):**
2 RCTs,153 with 1260 patients,
Rifaximin 550 mg 3x/day for 14 days was more efficacious than placebo
(RR 0.92; 95% CI 0.86 to 0.98)

**Re-treatment trial:**
2435 patients treated with open label rifaximin
→ 1074 (44.1%) responders
→ 692 (64.4%) relapse;
→ 636 randomized rifaximin (n = 328) vs. placebo (n = 308)
→ Response = decrease abdominal pain >30%, stool frequency >50%, ≥ 2 weeks
rifaximin: 38.1% vs. placebo 31.5% (p=0.03)

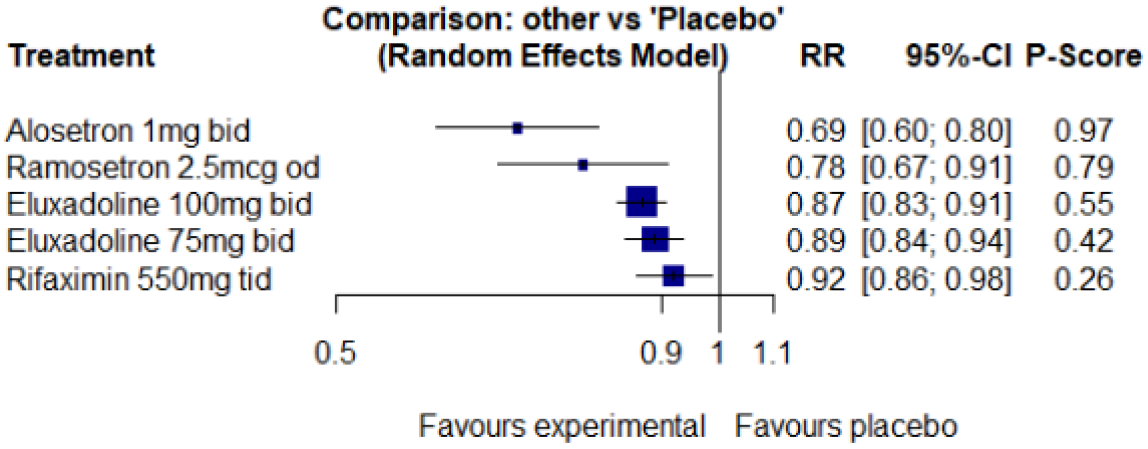
→ FDA approval (not approved in Switzerland for this indication)
→ Insel: Selektive Darm Dekontamination (SDD-capsules)
80mg gentamicin + 100 polymyxin 4xper day for 2-4 week

→ Alternatives: Norfloxacin, metronidazol, ciprofloxacin, tetracycline,
trimethoprim/ sulfamethoxazol

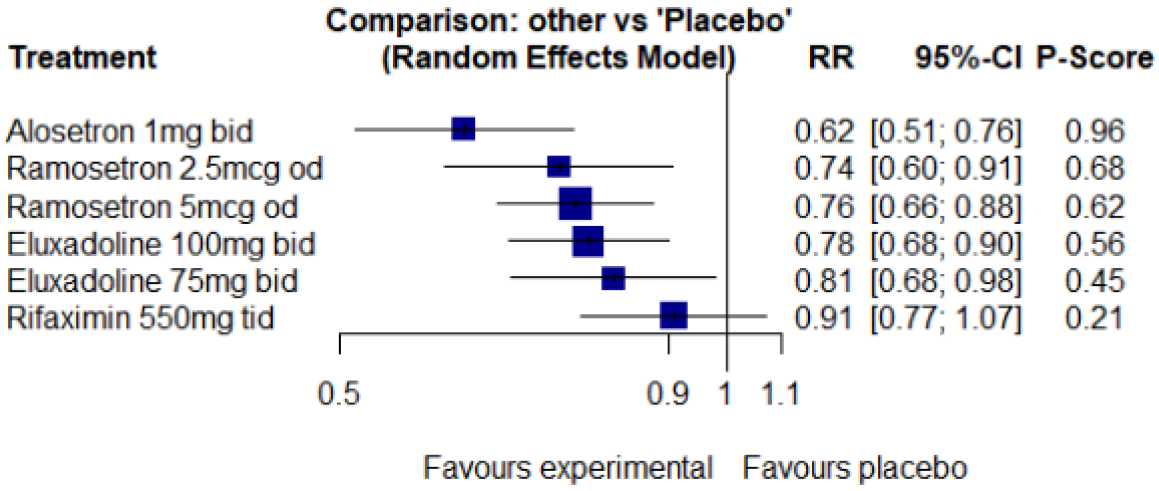
Pimentel et al., NEJM 2011;364:22
Lembo et al., Gastroenterology 2016;151:1113
Lauritano et al., Am J Gastroenterology 2008; 103:2031

# Network meta-analysis IBS-D

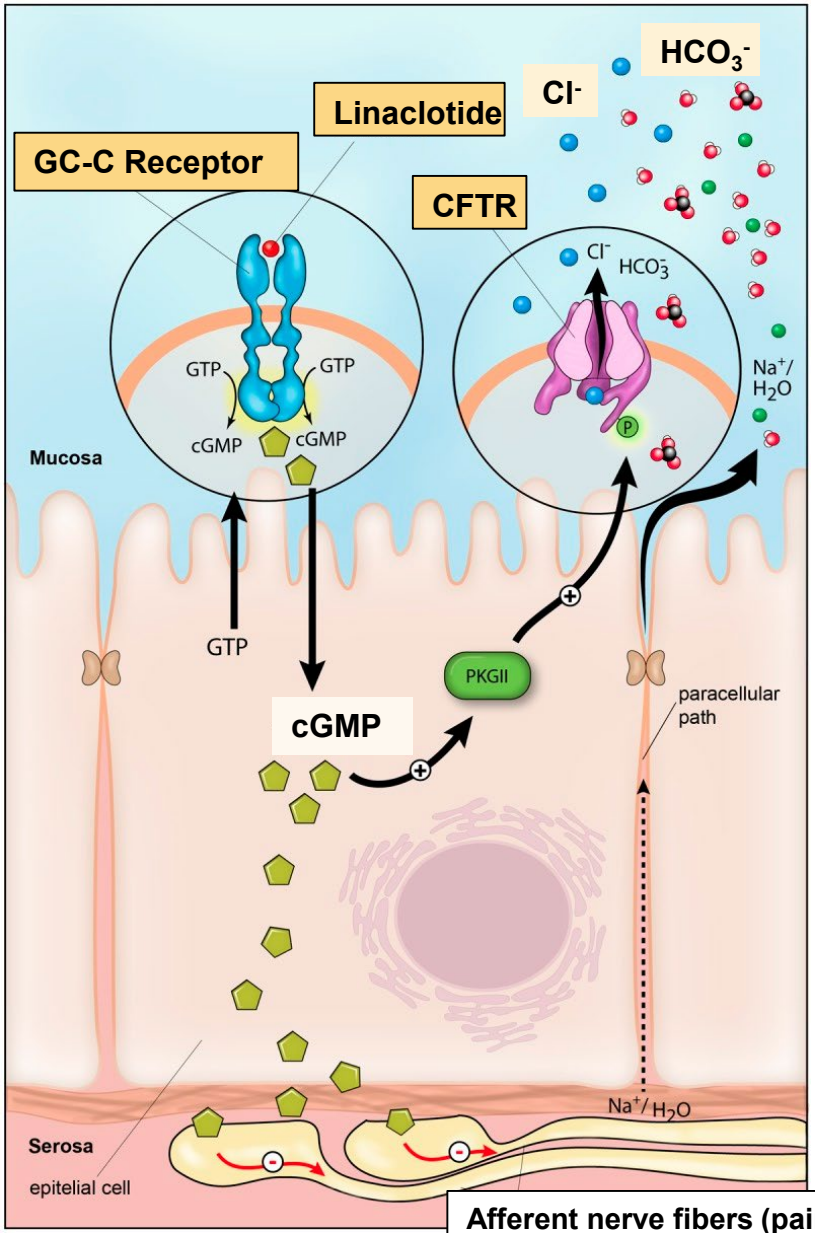
**Abdominal pain and stool consistency**




**Global Symptoms**



# Second line drugs IBS-C: Linaclotide




**Linaclotide**

- 14 amino acid peptide
- Related to hormones guanylin and uroguanylin

**Mechanism**

Intestinal lumen
Binding to GC-C-receptors

↓

In the cell: cGMP increase

↓

cGMP leaves the cell and inhibits afferent pain fibers

↓

Improvement in Abdominal pain

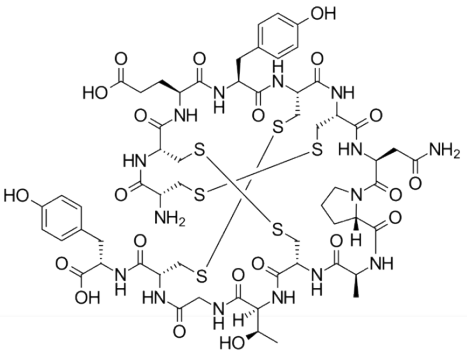
Secretion of Chlorid and bicarbonat via CFTR

↓

Improvement of constipation

Castro et al., Gastroenterology 2013
Lacy et al., Therap Adv Gastroenterol 2012; 5:233

# Second line drugs IBS-C
# Linaclotide, Constella®



Bioavailability: 0.1% (not resorbed)

**Linaclotide:** 5 RCTs with 3193 patients
FDA composite end point for IBS-C, consisting of
- Improvement in abdominal pain and
- Increase of ≥1 complete spontaneous bowel movement (CSBMs) per week from baseline

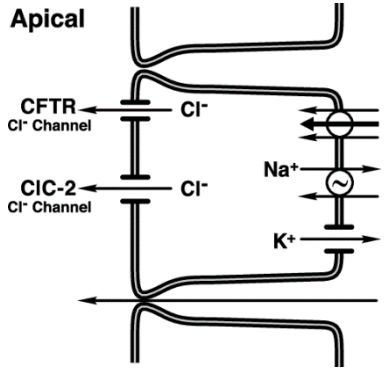
RR 0.82; 95% CI 0.78 to 0.87

**Plecanatide** (3 or 6 µg once a day) was also effective

**Linaclotide improves pain and constipation in IBS-C**

Rao et al., Am J Gastroenterol 2012; 107:1714
Chey et al., Am J Gastroenterol 2012; 107:1702
Johnston et al., Curr Med Res Opin 2013; 29:149

# Lubiprostone (Amitiza®)



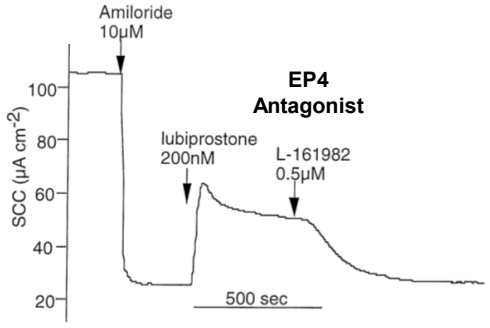

Derived from prostaglandin E1

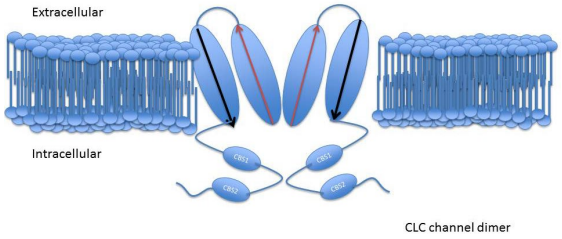
Almost not absorbed (acts locally, from the lumen)

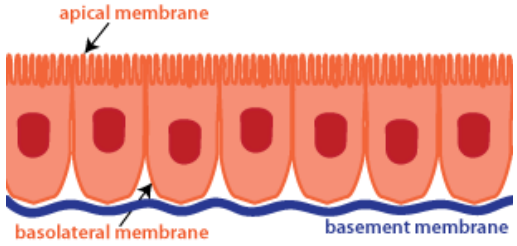
Activates **chloride channels**, stimulates secretion

Two potential targets:

- Chloride channel-2
  - → Activated on apical membrane → increased Cl- secretion
  - → Internalized on basolateral membrane → reduced reabsorption
- Activates prostaglandine E2 Rezeptor 4 (EP4) → cAMP
  - → activates the Cystic Fibrosis Transmembrance Conductance Regulator (CFTR)



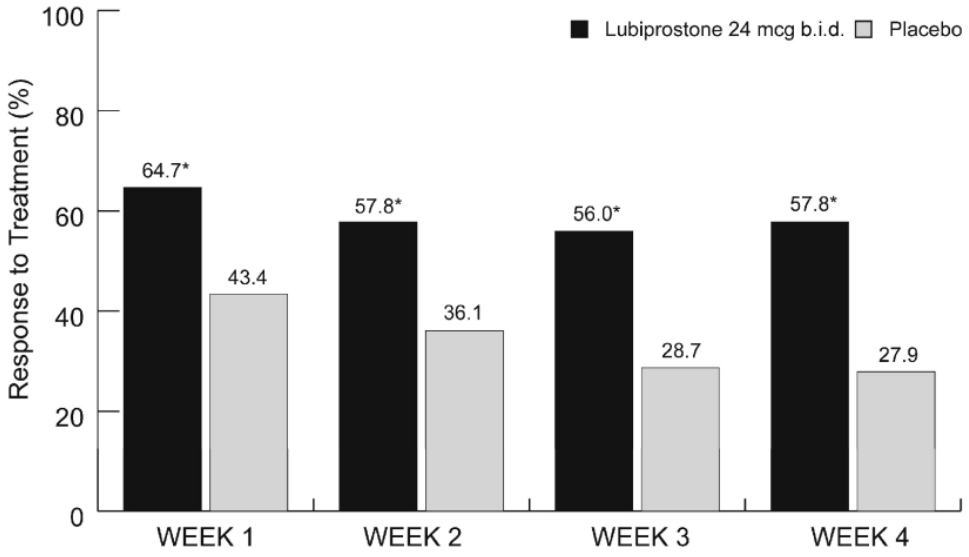

Cuppoletti et al., AJP Cell Physiol 2004; 287:C21173
Cuthbert, Br J Pharmacol 2011; 162:508
Wilson et al., Ther Adv Chronic Dis 2015, 6:40

# Lubiprostone (Amitiza®) - efficacy

Dosage: 24μg 2x per day po

Effective in 5 randomized controlled trials in chronic constipation, opioid induced constipation, irritable bowel syndrome (n>3400)

e.g.: 479 patients, 4 weeks: 63% vs. 32%
spontaneous bowel movement after medication intake

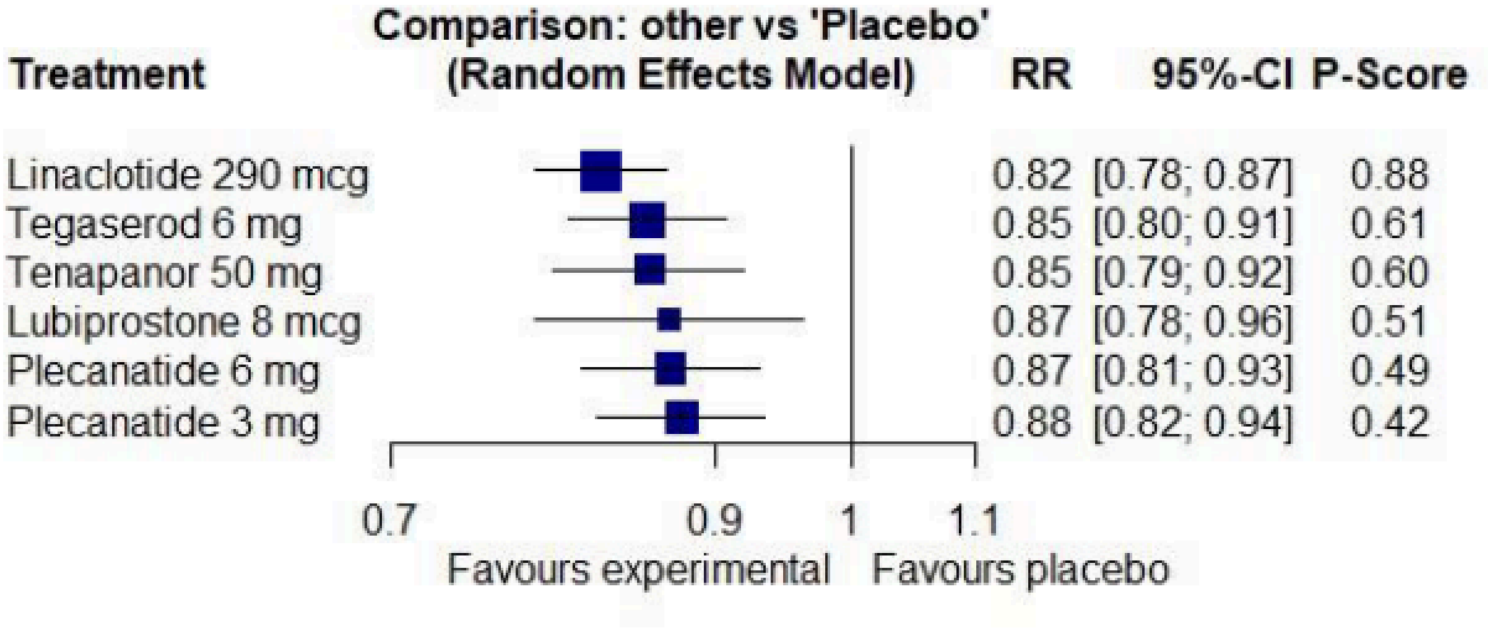



**≥3 spontaneous bowel movements per week**


Cuppoletti et al., AJP Cell Physiol 2004; 287:C21173
Cuthbert, Br J Pharmacol 2011; 162:508
Wilson et al., Ther Adv Chronic Dis 2015, 6:40

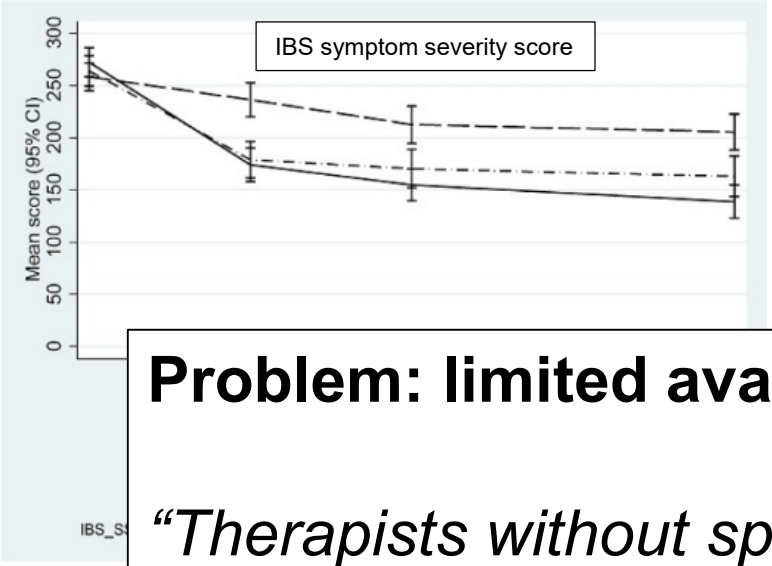
# Network Meta-Analysis IBS-C

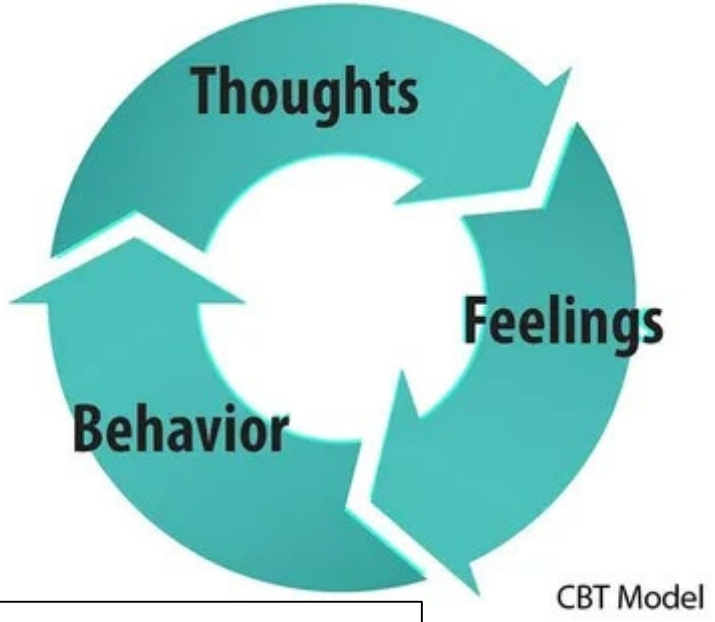
Composite endpoint improvement in abdominal pain and ≥1 increase in Complete spontaneous bowel movements per week




Tenapanor: Na-H exchange inhibitor
Tegasorid is only available for severe IBS
Prucaloprid has not been tested for IBS

# IBS specific cognitive behavioural therapy (CBT)



CBT Model

**Problem: limited availability, also in Bern**

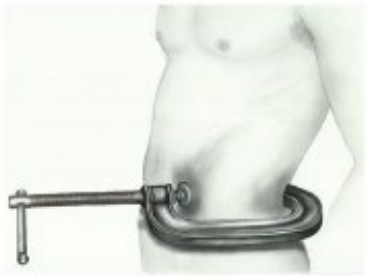
*"Therapists without specific IBS training tend to default to using mental health treatments, which can disengage patients with IBS.»*

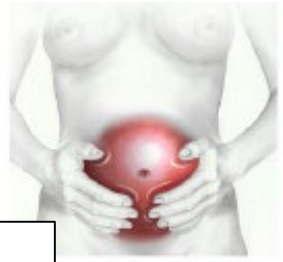
15 trial
- CBT

- Face-face CBT (10 RCTs, 930 patients, RR 0.62; 95% CI 0.48 to 0.80)
- Self-administered or minimal contact CBT (4 trials, 434 patients, RR 0.61; 95% CI 0.45 to 0.83)
- Therapist-delivered CBT over the telephone (1 RCT, 373 patients, RR 0.50; 95% CI 0.29 to 0.84)
- Group CBT (2 trials, 50 patients, RR 0.41; 95% CI 0.19 to 0.91)

ACTIB trial: Everitt et al, Gut 2019; 68:1613

# IBS specific „hypnotherapy“





6-12 weekly sessions of 30-60 min
- Patient education
- Visualizing intestinal problems using personal imagery
- Re-gaining control of intestinal function
- Diaphragmatic breathing, techniques overcoming anxiety, fear

**Referral for IBS-specific CBT or hypnotherapy for refractory symptoms after 12 months of treatment**
***→ Why not earlier??***

6 RCT
- RR
  cor
- RR
  compared with a waiting list control

One large open label trial with 1000 patients:
- 76% met primary outcome (IBS-SSS drop >50%) after therapy accompanied by improvements in pain, anxiety, QoL

Vasant et al., Neurogastroenterol Motil 2019; 31:e13573
Miller et al, AP&T 2015; 41:844

# Refractory/ severe IBS

Imprecisely defined as a composite of

- Severe patient-reported gastrointestinal and extraintestinal symptoms
- High degree of disability
- Pronounced illness-related perceptions and behaviours
- Insufficient response to conventional treatments
- High health care utilisation.

Approximately 25% of patients.
Risk of incorrect diagnosis is (somewhat) higher → review of diagnosis
At high risk for inappropriate interventions.
→ multi-disciplinary approach.
→ «augmentation»: duloxetin (SNRI) + gabapentin
→ Dietician, psychotherapist

# Emerging drugs and therapeutics in IBS in clinical trials

| | |
|---|---|
| Minesapride | 5-HT4 agonist) |
| Ebastine | Histamin receptor-1 antagonist |
| Elobixibat | Bile acid transport inhibitor |
| Mizagliflozin | Sodium-glucose cotransporter-1 inhibitor |
| Delayed-release linaclotide | |
| Olorinab | Cannabinoid type-2 receptor agonist |

Absorbing gel


Exoperistalsis device

Vasant et al, Gut 2021; 70:1214

**Thank you for your attention!**