Approach to Irritable Bowel Syndrome

The Good, the Bad and the Uncertain

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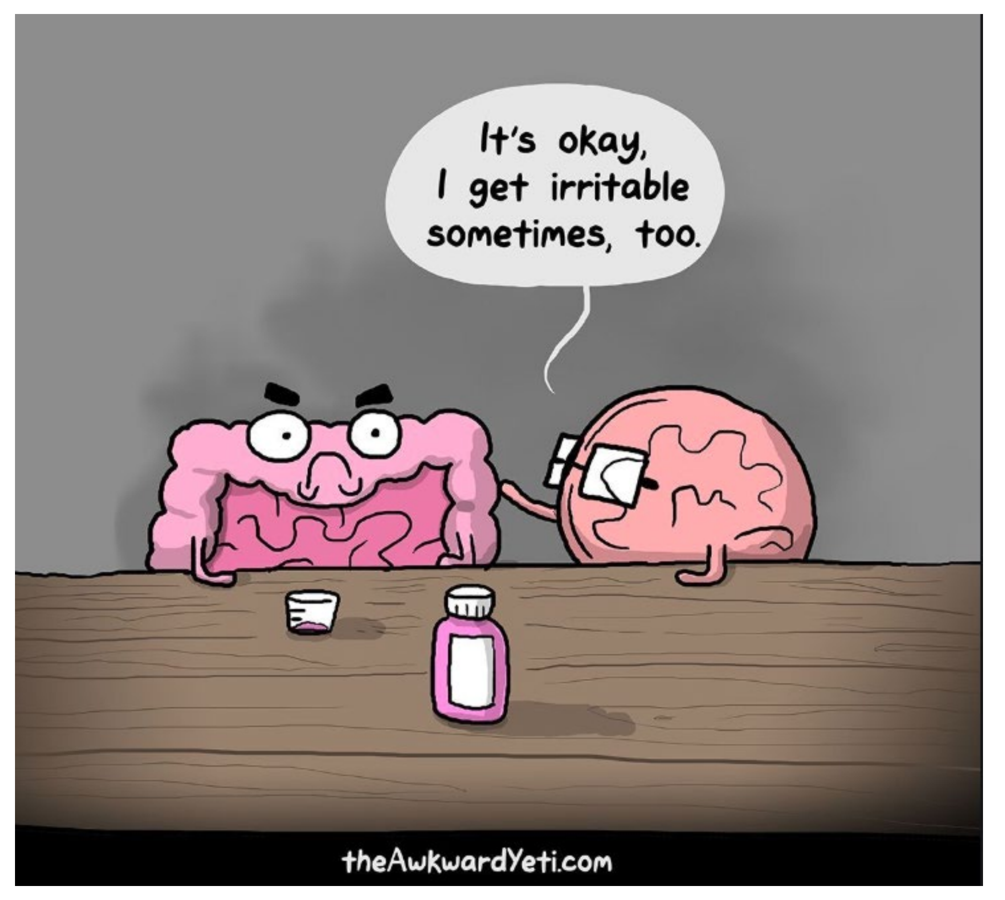
Disclosures

- Dr. Karen Toews
  - No commercial or financial conflicts of interest to declare
- Dr. Grace Frankel
  - No commercial or financial conflicts of interest to declare
- We just like to talk about poop



1. *Review* the Rome diagnostic criteria for IBS and question whether IBS is a diagnosis of exclusion.
2. *Explore* the brain-gut/gut-brain hypothesis as the proposed pathophysiology of irritable bowel syndrome (IBS)
3. *List* the pharmacological treatments for IBS-C and IBS-D and explore relative efficacy
4. *Discuss* 2 herbal product options for treatment of IBS
5. *Summarize* 4 IBS management PEARLS for primary care

Learning Objectives

According to the Bristol Stool Chart, what type of poop is this?

Type 1 = severe constipation

Separate, hard lumps, like nuts (hard to pass)

slido #POOPTALK

ROME IV Criteria

- Patient has recurrent abdominal pain (≥1 day per week, on average, in the previous 3 mo), with an onset ≥6 mo before diagnosis
- Abdominal pain is associated with at least two of the following three symptoms:

  Pain related to defecation
  Change in frequency of stool
  Change in form (appearance) of stool

- Patient has none of the following warning signs:
  Age ≥50 yr, no previous colon cancer screening, and presence of symptoms

  Recent change in bowel habit
  Evidence of overt GI bleeding (i.e., melena or hematochezia)
  Nocturnal pain or passage of stools
  Unintentional weight loss
  Family history of colorectal cancer or inflammatory bowel disease

  Palpable abdominal mass or lymphadenopathy
  Evidence of iron-deficiency anemia on blood testing
  Positive test for fecal occult blood

N Engl J Med2017;376:2566-78

Figure 1: Bristol Stool Form Scale to Identify IBS Subtype

Type 1
Type 2
Type 3
Type 4
Type 5
Type 6
Type 7

% Bowel movement hard or lumpy

100
75
50
25
0

Bristol types 1 or 2

IBS-C

IBS-U

1 and 2
plus
6 and 7

IBS-M

IBS-D

Bristol types 6 or 7

0
25
50
75
100

% Bowel movement loose or watery

Constipated >25% and <25% diarrhea
IBS-C

A bit of everything (>25% for both)
IBS-M

Diarrhea >25% and <25% constipation
IBS-D

From Pinto-Sanchez MI. Irritable Bowel Syndrome Chapter In CTC [Accessed May 2020]

Gut-Brain or Brain-Gut

Genetic predisposition and environmental factors (including modeling, reward behavior, and cultural factors)

↓ → CNS alterations (stress pathway activation, anxiety, depression)

↓ Alterations in gut epithelium and microbiome, increased risk of intestinal infection

Changes in tight junction and intestinal permeability

↓

Localized inflammation, edema, or both; infiltration of inflammatory cells (e.g., mast cells, eosinophils); release of cytokines

↓

Changes in visceral neuromuscular function (→ CNS alterations)

↓

Development of IBS symptoms

Gutsy move ...for a brain!

N Engl J Med 2017;376:2566-78

Brain-Gut or Gut-Brain

Infection, inflammation, food antigens, and medications

↓

Changes in tight junction and intestinal permeability

↓

Alterations in gut microbiome

↓

Infiltration of inflammatory cells, changes in immunocyte function, cytokine release

↓

Development or exacerbation of IBS symptoms ↔ Changes in CNS function (new-onset anxiety, depression, somatization)

THE GUT-BRAIN CONNECTION

N Engl J Med 2017;376:2566-77

A Diagnosis of Exclusion?

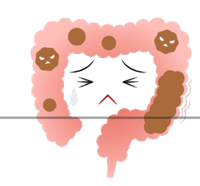
National guidelines for IBS management state that in a patient who has symptoms meeting the Rome IV criteria, with no alarm features, the **physician should make a POSITIVE diagnosis of IBS** without resorting to a battery of tests.

Ordering a panel of blood tests routinely is unsupported by the evidence.

Am J Gastroenterol 2014;109

Which of following diagnostic test(s) is/are important to order for a patient you suspect has IBS?

1. Colonoscopy
2. Celiac Screen
3. Fecal calprotectin
4. CBC
5. Food allergy testing
6. None of the above



Canadian IBS Guideline 2019 Recommendations:

Statement 1: We suggest IBS patients have serological testing to exclude celiac disease.

GRADE: Conditional recommendation, low-quality evidence. Vote: strongly agree, 50%; agree, 50%

Data from seven case-control studies showed a greater likelihood of having positive celiac antibodies among patients with IBS compared with controls without IBS (odds ratio [OR] 2.94; 95% CI, 1.36–6.35)

Statement 4: We recommend AGAINST IBS patients <50 years of age without alarm features ROUTINELY having a colonoscopy to exclude alternate diagnoses.

GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 92%; agree, 8%

Statement 5: We suggest AGAINST IBS patients <50 years of age with alarm features ROUTINELY having a colonoscopy to exclude alternate diagnoses.

GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 25%; agree, 75%

Diagnostic algorithm

Patient has chronic symptoms of abdominal pain associated with constipation, diarrhea, or both, with or without bloating

↓

Obtain history and perform physical examination (including medical, surgical, and dietary history and digital rectal examination)

↓

If normal physical examination and no warning signs in history, apply Rome IV criteria

↓

Positive diagnosis of IBS is made

↓

- Consider limited testing (CBC, CRP level, celiac serologic test, fecal calprotectin level)
- Use Bristol Stool Form Scale to identify IBS subtype

↓

Initiate treatment based on predominant symptom

N Engl J Med 2017:376

Celiac serology
Colonoscopy if new onset and ≥50 y*

+ve → Treat organic disease

-ve

Soluble fibre

Peppermint oil†

Antispasmodics§

Focus on predominant bowel habit

IBS-D
- Low FODMAP diet
- Probiotics
- TCA
- Eluxadoline
- CBT or hypnotherapy

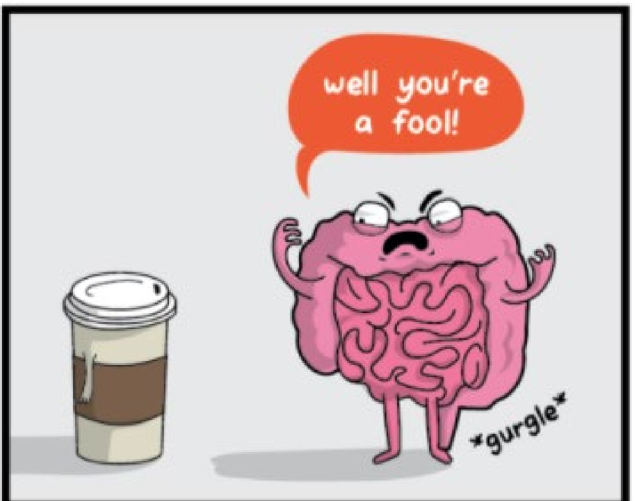
IBS-M or IBS-U
- Low FODMAP diet
- Probiotics
- TCA
- CBT or hypnotherapy

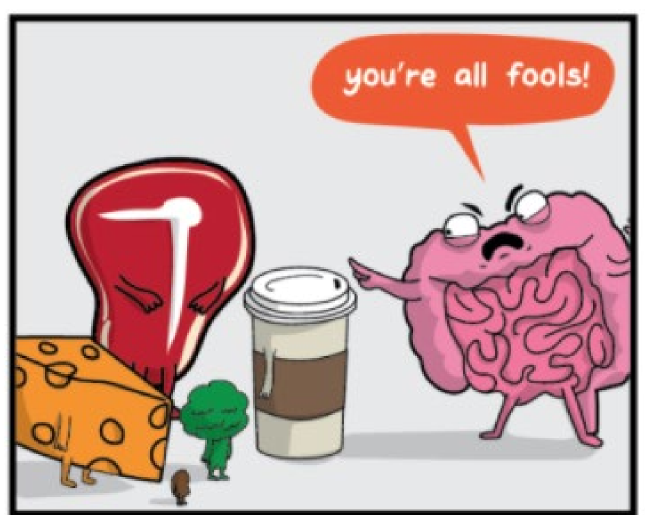
IBS-C
- Linaclotide
- SSRI
- Lubiprostone
- CBT or hypnotherapy

Most patients, most of the time

Careful discussion w/ patients re: options

NOT RECOMMENDED TREATMENTS
- Gluten-free diet
- Wheat bran supplementation
- Herbal remedies
- Acupuncture
- Continuous loperamide
- Cholestyramine
- Osmotic laxatives
- Prucalopride





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Treatment of IBS

So Many Drugs…….What Do I Pick?

Irritable Bowel Syndrome

Treatment

Abdominal Pain

Antispasmotics
Dicyclomine (Bentylol®)
Hyoscine (Buscopan®
Pinaverium (Dicetel®)
Trimebutine (Modulon®)

Diarrhea

Loperamide (Immodium®)
Diphenoxylate/atropine (Lomotil®
Cholestyramine (Olestyr®)
Eluxadoline (Viberzi®)
Rifaxamin (Zaxine®)

Constipation

Psyllium + Fluids
PEG
Senna/bisacodyl
Lubiprostone*
Linaclotide
Plecanatide*
Tenapanor
?Prucalopride

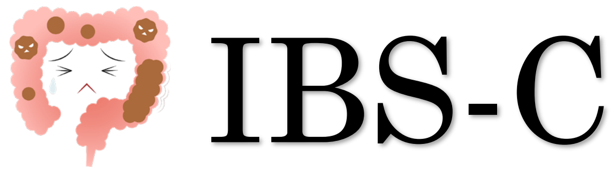
Pain AND Diarrhea
Tricyclic antidepressants

Pain AND Constipation
SSRIs – **paroxetine, fluoxetine and citalopram** have been investigated for IBS

*Not available in Canada

Which of the following medications is a prokinetic drug for IBS-C that has a warning for increased risk of suicide/suicidal ideation?

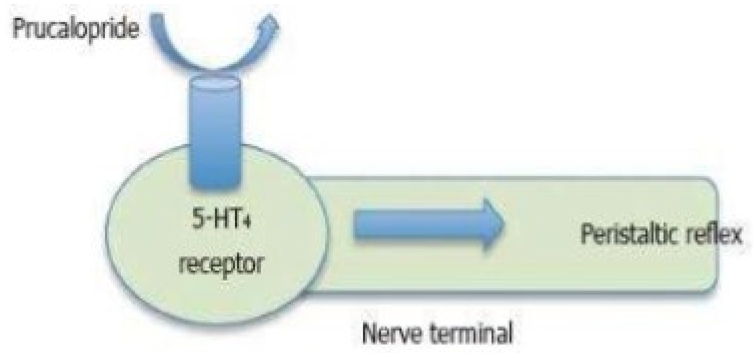
a) Linaclotide
b) Tenapenor
c) Loperamide
d) Prucalopride



IBS-C

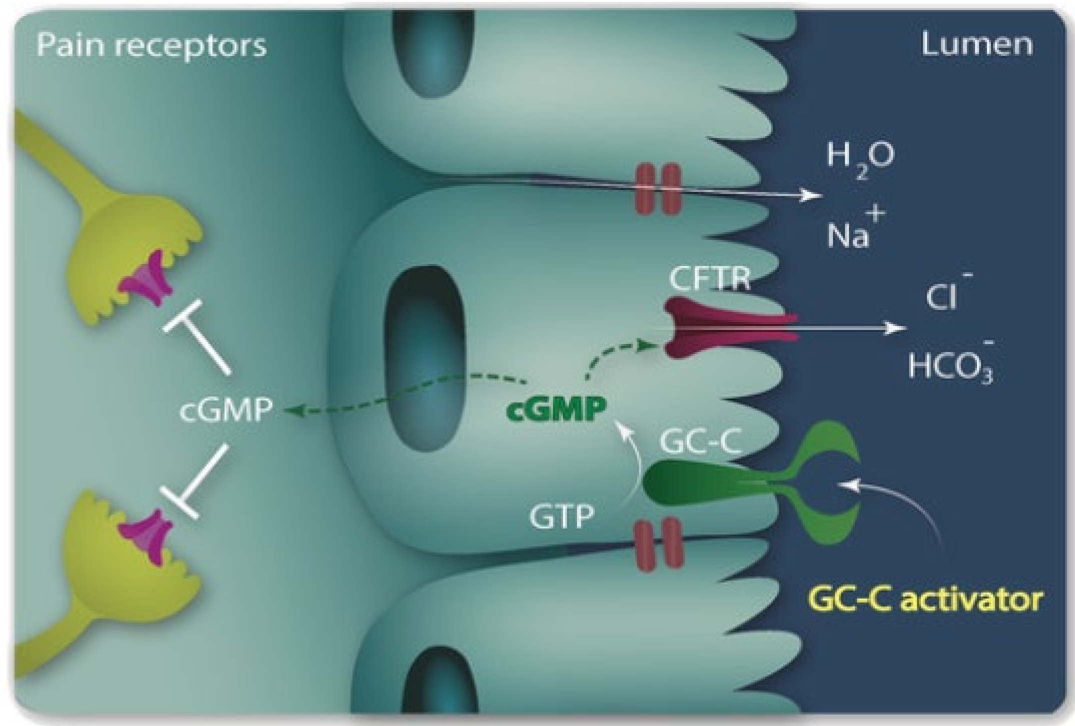
Prucalopride RESOTRAN

Serotonin (5HT4) agonist = peristalsis in gut (prokinetic agent)



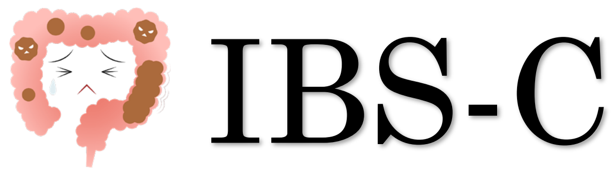
World J Gastrointest Pharmacol Ther. May 6, 2016; 7(2): 334-342

Linaclotide CONSTELLA & Plecanatide TRULANCE



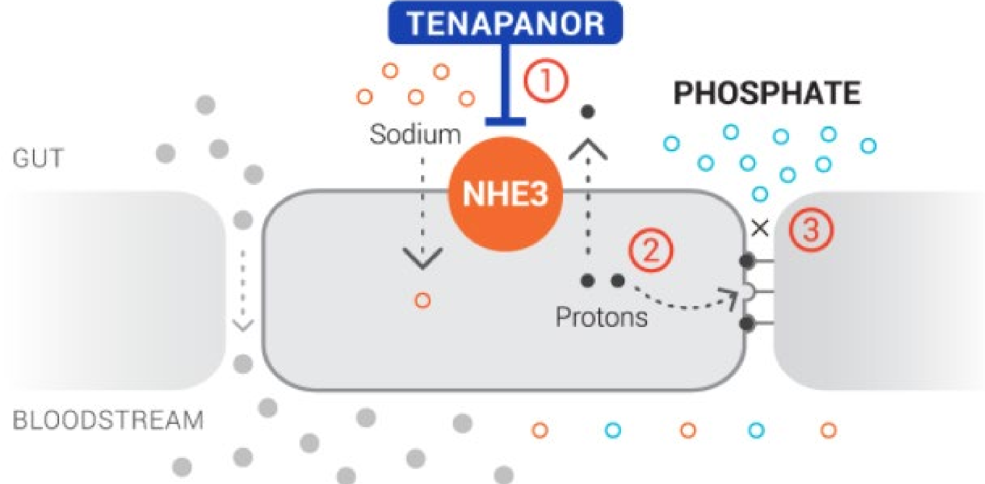
Advanced Drug Delivery Reviews. 101. 10.1016/j.addr.2016.01.010.

Guanylate Cyclase C (GC-C) agonist = chlorine and bicarb into lumen which increases intestinal fluids. cGMP may also reduce pain pathway



IBS-C

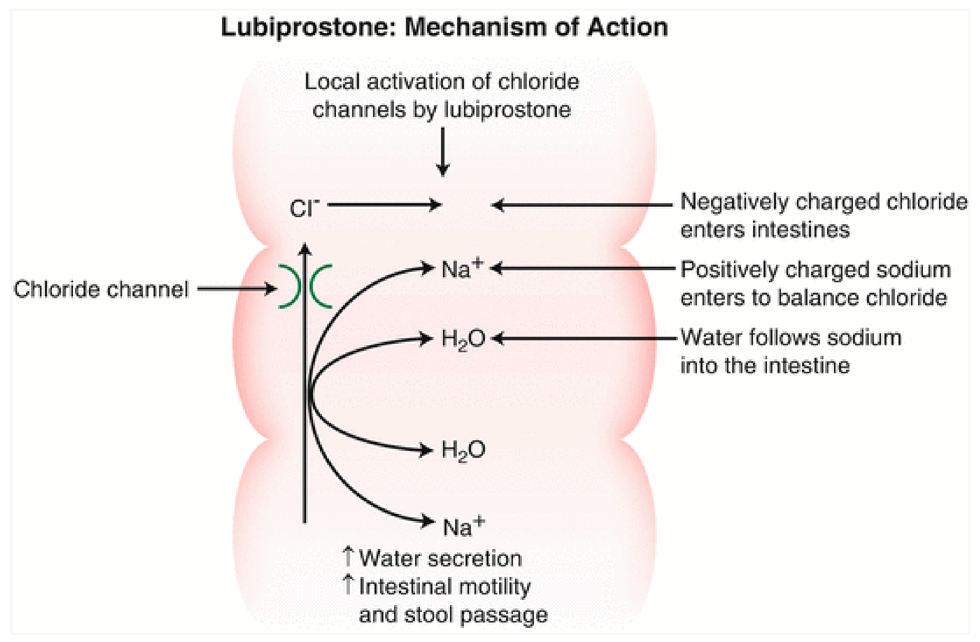
Tenapanor IBSRELA



* King et al. Inhibition of sodium/hydrogen exchanger 3 in the gastrointestinal tract by tenapanor reduces paracellular phosphate permeability. *Sci Transl Med* 10, eaam6474. DOI: 10.1126/scitranslmed.aam6474.

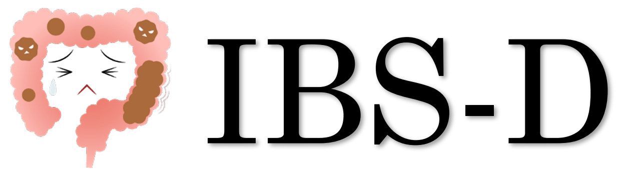
Inhibits sodium/H+ exchanger = sodium, phosphate and water are excreted (softening stools, also to ↓phosphate in CKD)

Lubiprostone AMITIZA



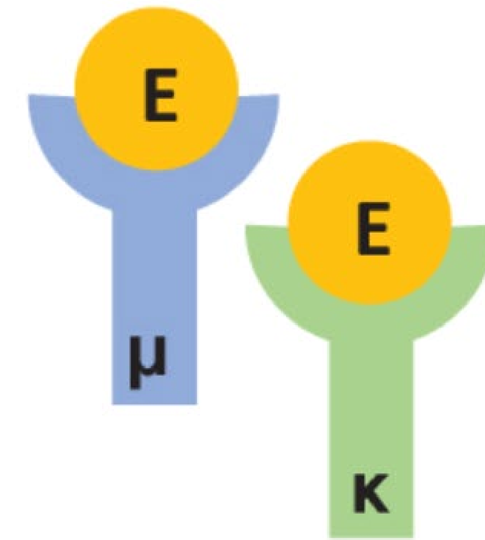
Chloride channel activator = draws in water to soften stool

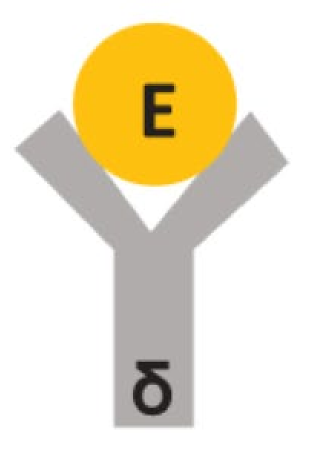
Irritable Bowel Syndrome with Constipation. In: Rose, MD, MSEd S. (eds) Constipation. Springer, New York, NY

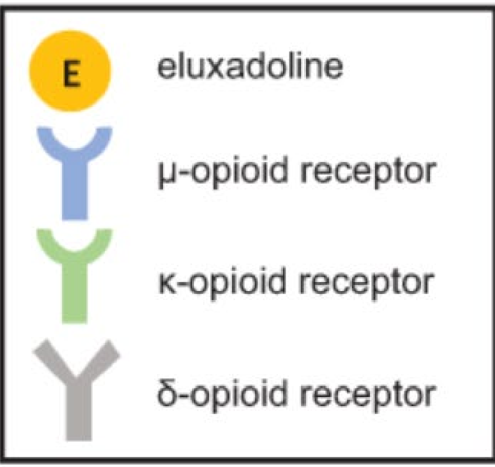


IBS-D

Eluxadoline VIBERZI







Slows gut motility (μ), reduces pain (κ)

Modulates μ-receptor activity to prevent constipation

Drug Design, Development and Therapy 2020:14 1391–1400

Do drugs for IBS work?

TOOLS FOR PRACTICE

Antidepressants for irritable bowel syndrome

Paul Fritsch MD CCFP Michael R. Kolber MD CCFP MSc Christina Korownyk MD CCFP

April 2020

18 RCTs (n=1127) with the majority of patients being women

Global improvement in IBS symptoms 57% TCAs vs 26% placebo (NNT=5), SSRIs 55% vs 33% (NNT=5)
Abdominal pain improvement TCAs 59% vs 28% (NNT=4), SSRIs 45% vs 26% but not significant

Side effects? Worse with TCAs (drowsiness, dry mouth) NNH=7
SSRIs 37% vs 27% not significant

Do drugs for IBS work?

Efficacy and Tolerability of Guanylate Cyclase-C Agonists for Irritable Bowel Syndrome with Constipation and Chronic Idiopathic Constipation: A Systematic Review and Meta-Analysis

Am J Gastroenterol. 2018 March ; 113(3): 329–338

8 linaclotide and 7 plecanatide trials included (n=10,369 patients)
For IBS-C primary outcome is decrease in pain ≥30% in past 24h with increase in CSBM ≥1 per week for half the weeks in a 12-week follow-up period

Linaclotide: OR 2.43 (1.48-3.98) NNT=6
Plecanatide: OR 1.87 (1.47-2.38) NNT=9 versus placebo
Side effects? Diarrhea linaclotide NNH=32, plecanatide NNH >100
Note when I crunch the numbers it's more like **NNH =18-24** linaclotide, **NNH=62** plecacatide (there were a couple studies with no events)

Comparative efficacy studies sparse/small
(but several SR/MA protocols underway)

Drugs for IBS available in Canada

Drug	Indication	Dose	Cost/Coverage
Prucalopride (Resotran®) 5HT4 agonist	Chronic Idiopathic Constipation (NOT for IBS-C)	2mg daily	Generic: $100/month (Not covered)
Linaclotide (Constella®) GC-C agonist	IBS-C	290mcg daily 30 min prior to breakfast	$180/month (Not covered)
Tenapanor (Ibsrela®) NHE3 inhibitor	IBS-C	50mg BID	$190/month (Not covered)
Eluxadoline (Viberzi®) Opioid receptor modulator	IBS-D	100mg BID	$160/month (Not covered)
Rifaxamin (Zaxine®) antibiotic	IBS-D (SIBO?)	550mg TID x 14 days	$350/14 day treatment Not Covered for SIBO/IBS (Part 3 for hepatic encephalopathy)
Hyoscine (Buscopan®)	Abdominal pain/spasm	10mg	$22/60 tabs **Covered Part 1**
Pinaverium Bromide (Dicetel®)	Abdominal pain/spasm	50-100mg TID with meals	Generic $30-60/month **Covered Part 1**
Diphenoxylate/atropine (Lomotil®)	Abdominal pain/spasm	5mg initial, then 2.5mg after each loose BM	$33/60 tabs Not covered
TCAs and SSRIs	Pain with either constipation (TCAs) or diarrhea (SSRIs)	Various, lower doses than antidepressant doses	Cheap <$1/day **Covered Part 1**

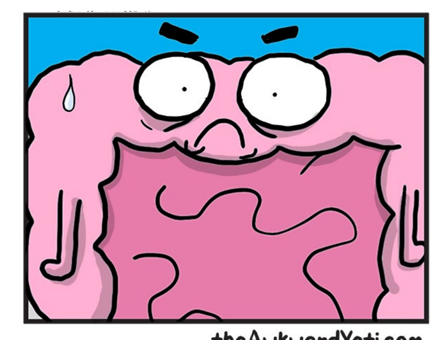
True or False:
Essential oil of peppermint (5 drops PO TID) is an effective therapy for IBS

a) True
b) False

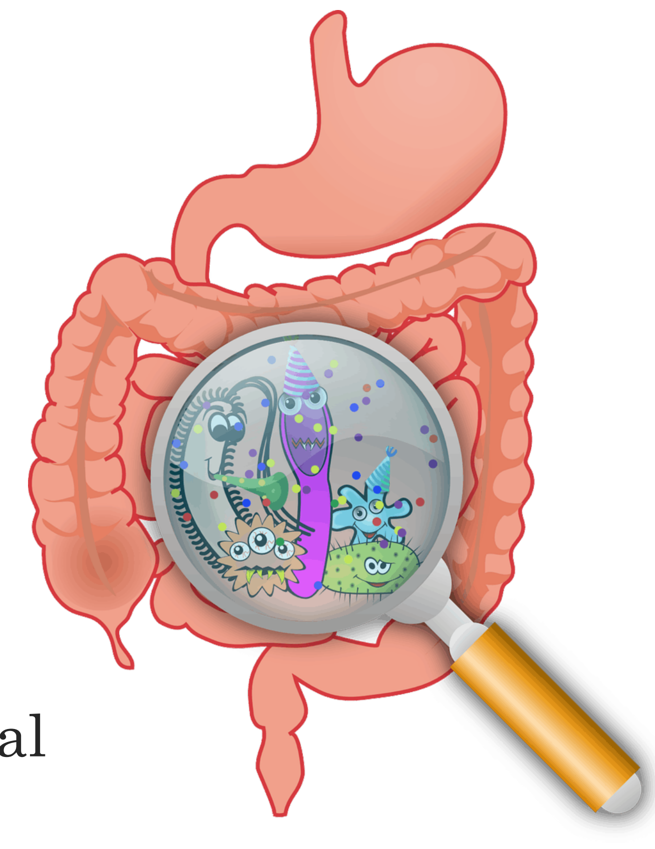
slido #POOPTALK

Peppermint Oil?

- SR/MA 2019 BMC Complement Altern Med. 2019 Jan 17;19(1):21
  - 7 studies (n=835); follow-up period ranged 2-12 weeks in duration
  - Peppermint oil (enteric coated) ?dose – who knows (usually 0.2-0.4mL in EC caps TID between meals)
  - **Global improvement in IBS symptoms:** ~60% peppermint vs 25% placebo (NNT=3)
  - **Improvement in abdominal pain:** 53.9% vs 30.3% (NNT=5)
  - **Side effects?** Heartburn, peppermint taste (limited safety data reported) – other sources estimate NNH=7 (RxFiles)
- Cost? $20-$40/month
- **PEARL:** Get ENTERIC COATED capsules! Essential oils = very irritating to the stomach!



Probiotics

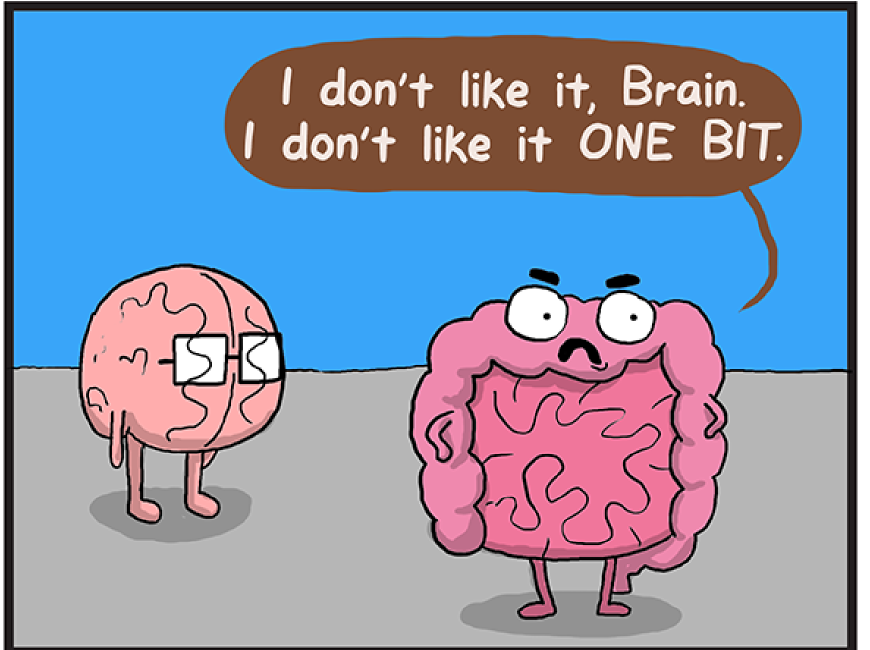


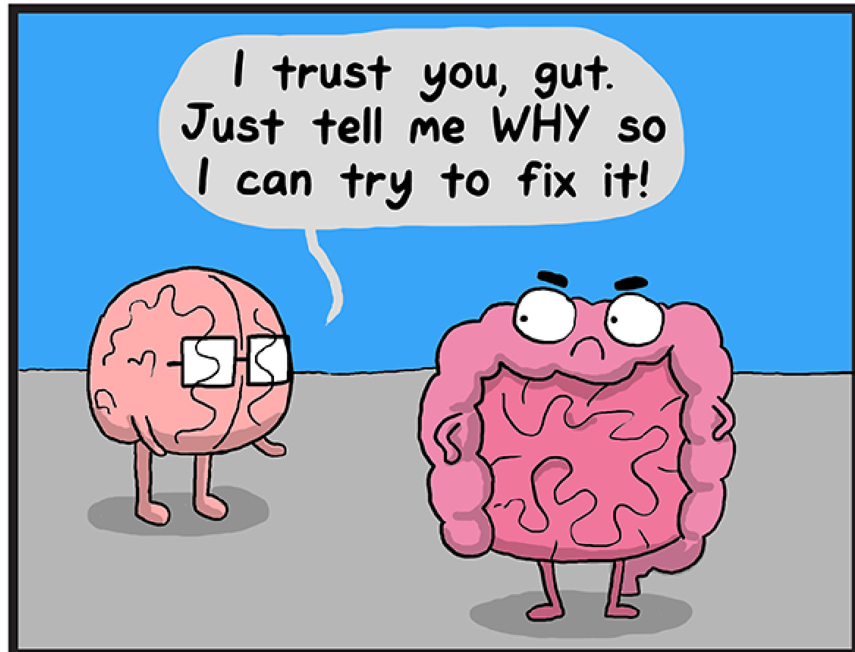
- SR-MA 2014 Am J Gastroenterol 2014; 109:1547–1561
  - 43 RCTs included analyzing prebiotics, probiotics and symbiotic in IBS and CIC
  - Probiotics for IBS: **RR 0.79 (95% CI 0.70-0.89)** for global improvement in symptoms vs placebo
    - Most effective for abdominal pain SMD -0.25, bloating SMD -0.15 and flatulence SMD -0.23 – small effect size
  - Concluded that which specific strains/species are unclear due to variability between studies
    Note high heterogeneity I^2=72%
  - Not enough data on pre-biotic and synbiotics

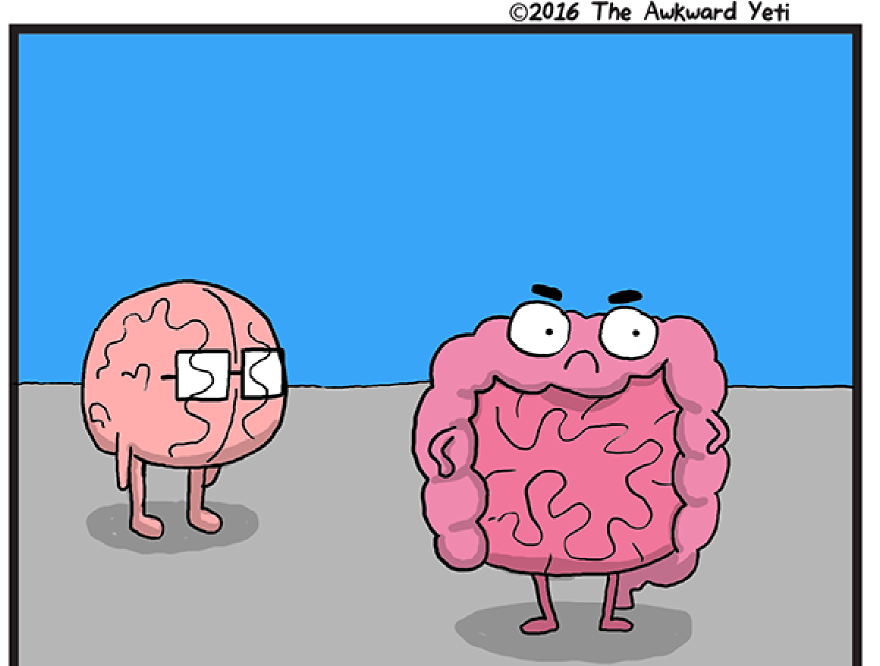
4 IBS PEARLS for Primary Care

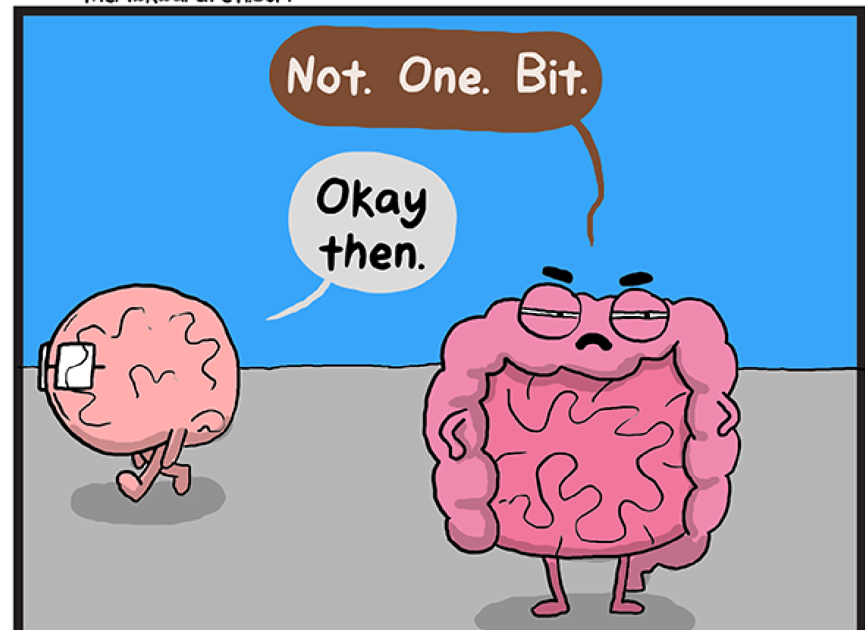
1. Be BRAVE! Make a **POSITIVE DIAGNOSIS of IBS**
2. Use the **Brain-Gut/Gut-Brain hypothesis** when counseling patients.
3. Most drugs for IBS have a **NNT of 4-8ish** but the new ones are currently **expensive and not covered**
4. **Peppermint oil works**! But use enteric coated capsules! Probiotics are an option too ☺

Questions?









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