



# GERD and Irritable Bowel Syndrome



Internal Medicine: Comprehensive Review and Update  
June 10, 2021

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# Disclosures

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- Consultant for Arena, Boston Pharmaceuticals, Gelesis, GI Supply, and Takeda/Shire
- Grant support from the NIH NIDDK



# Learning Objectives

- Understand the best approach to diagnostic testing in GERD
- Know the ins and outs of PPI therapy
- Understand the plusses and minuses of non-pharmacologic treatment of IBS
- Understand the brain-gut connection in IBS





# Part I: Gastroesophageal Reflux Disease (GERD)

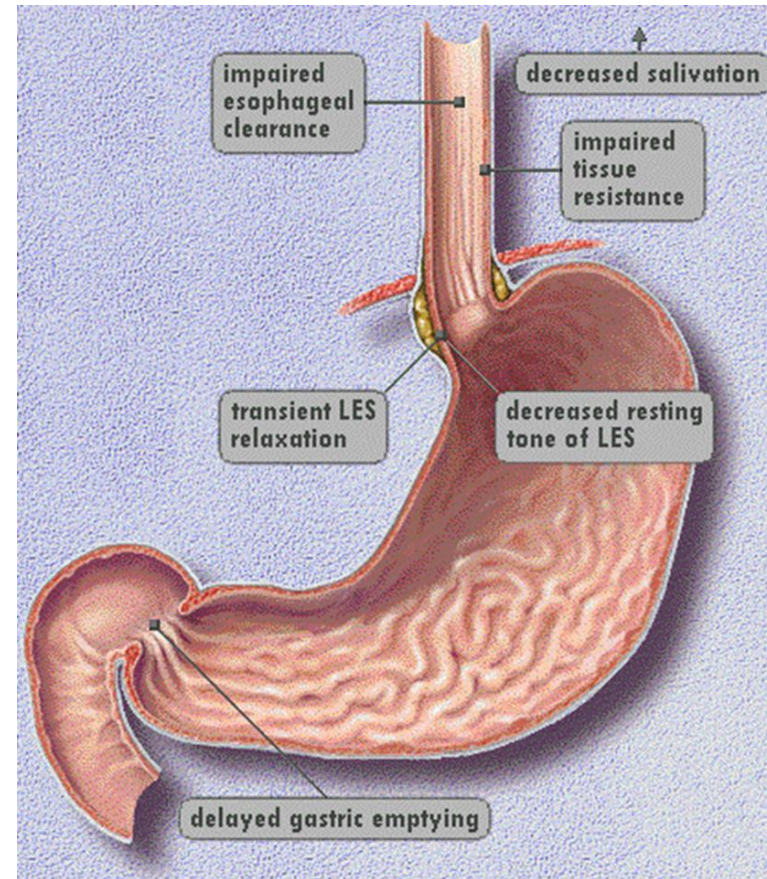


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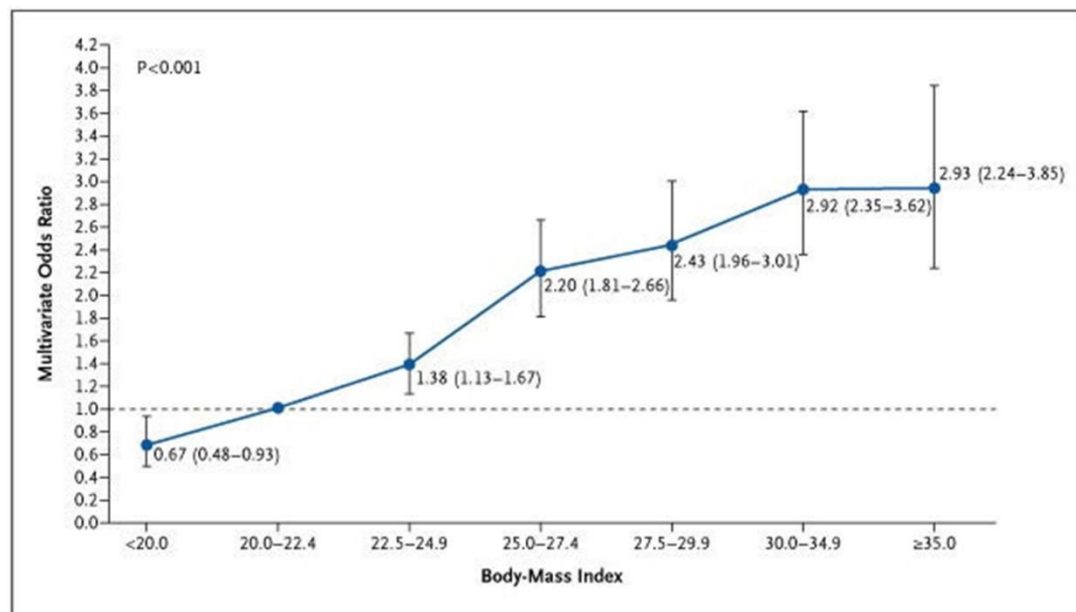
# Definitions

- GERD develops when the reflux of stomach contents causes symptoms/complications
  - Reflux that is not troublesome is not GERD
  - “Troublesome”: mild symptoms 2 or more times/week or severe symptoms 1 or more times/week
- Hallmark symptom of GERD is heartburn
- GERD is the most common GI diagnosis in your clinic



# Risk factors for GERD

- Obesity



- Smoking

- Menopausal hormone therapy (formerly HRT)

- Asthma/COPD

- Connective tissue disease (i.e. scleroderma)

- Medications (bisphosphonates)



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*N Engl J Med.* 2006 Jun 1;354(22):2340-8.

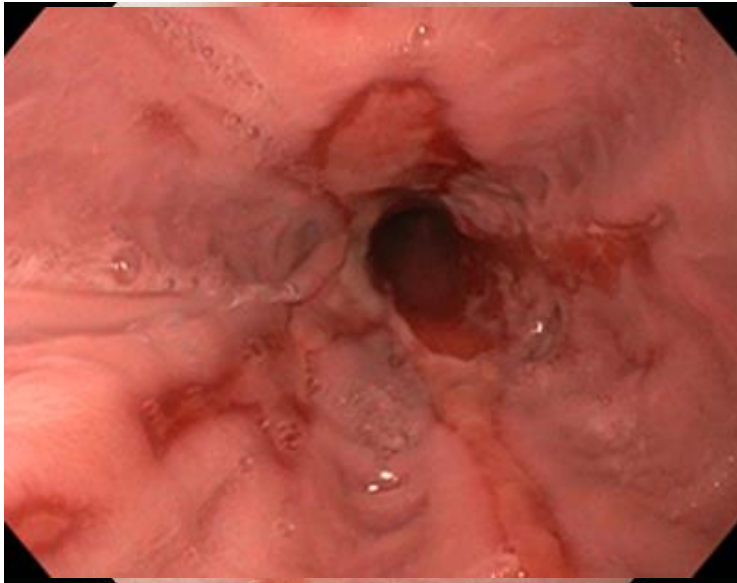


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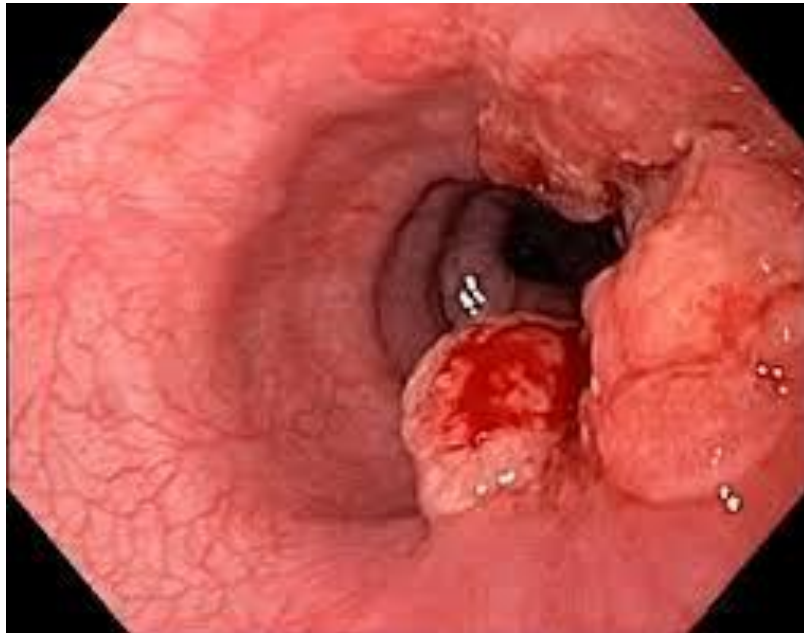
# Typical complications



- Erosive esophagitis
- Barrett's esophagus
  - Risk of progression to adenocarcinoma:
    - 0.12-0.38% per year
  - Screening interval  $\approx$  3 years
- Risk factors, chronic GERD symptoms plus:
  - Demographics: male, white, age >50
  - Lifestyle: smoking, central obesity
  - Family history: Barrett's esophagus or esophageal adenocarcinoma in 1<sup>st</sup> degree relative

# More serious complications

- Esophageal adenocarcinoma
  - Rates increasing rapidly in the western world
  - Increased risk with heartburn duration and frequency
  - Risk of development increases with age
  - Increasingly seeing in younger populations
  - Male-predominant (9:1)
  - White-predominant (5:1 compared to blacks)





# Oesophageal Adenocarcinoma

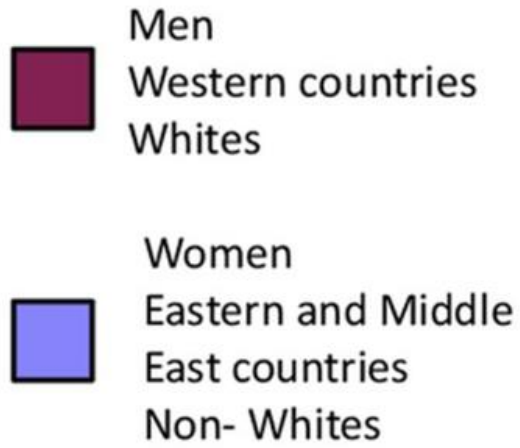
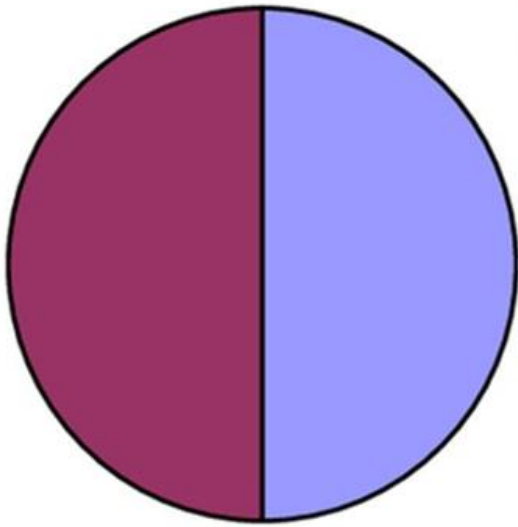
## Barrett's Oesophagus



## Erosive Oesophagitis



## GORD Symptoms\*



*Gut. 2014 Jul;63(7):1185-93.*

# GERD has atypical symptoms

- Chest pain
- Chronic cough
- Chronic laryngitis
- Asthma
- GERD often not the sole cause of atypical symptoms
- Atypical symptoms without concomitant heartburn/reflux unlikely to be due to GERD



# Diagnostic testing

- Clinical diagnosis: *young (<50 years old) with classic symptoms*)
- No alarm symptoms
  - Weight loss
  - Bleeding
  - Dysphagia
  - Family history of esophageal or gastric cancer
- Diagnostic/therapeutic acid suppression
  - Best sensitivity in patients with classic heartburn or chest pain
- Barium swallow? (NO → reflux common in healthy pts)
- Laryngoscopy (NO → laryngeal irritation in 80% healthy pts)
- Pulmonary symptoms (other than asthma): likely needs ambulatory pH testing

# When to order an upper endoscopy

- Useful with any alarm symptoms
- Can evaluate for mucosal disease but beware
  - Presence of erosive esophagitis (LA Grade B/C), Barrett's esophagus confirms GERD
  - EGD normal in 2/3 of patients with heartburn and regurgitation
- GERD symptoms to prompt EGD:
  - Refractory to treatment, long duration of symptoms
  - Atypical symptoms, dysphagia
- Demographics
  - Men with chronic (>5 years reflux) **PLUS**  $\geq 2$  of:
    1. >50 years
    2. White
    3. Central obesity
    4. Smoking
    5. Family history of Barrett's or esophageal cancer



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*J Gastrointest Surg.* 2014 Jan;18(1):26-33

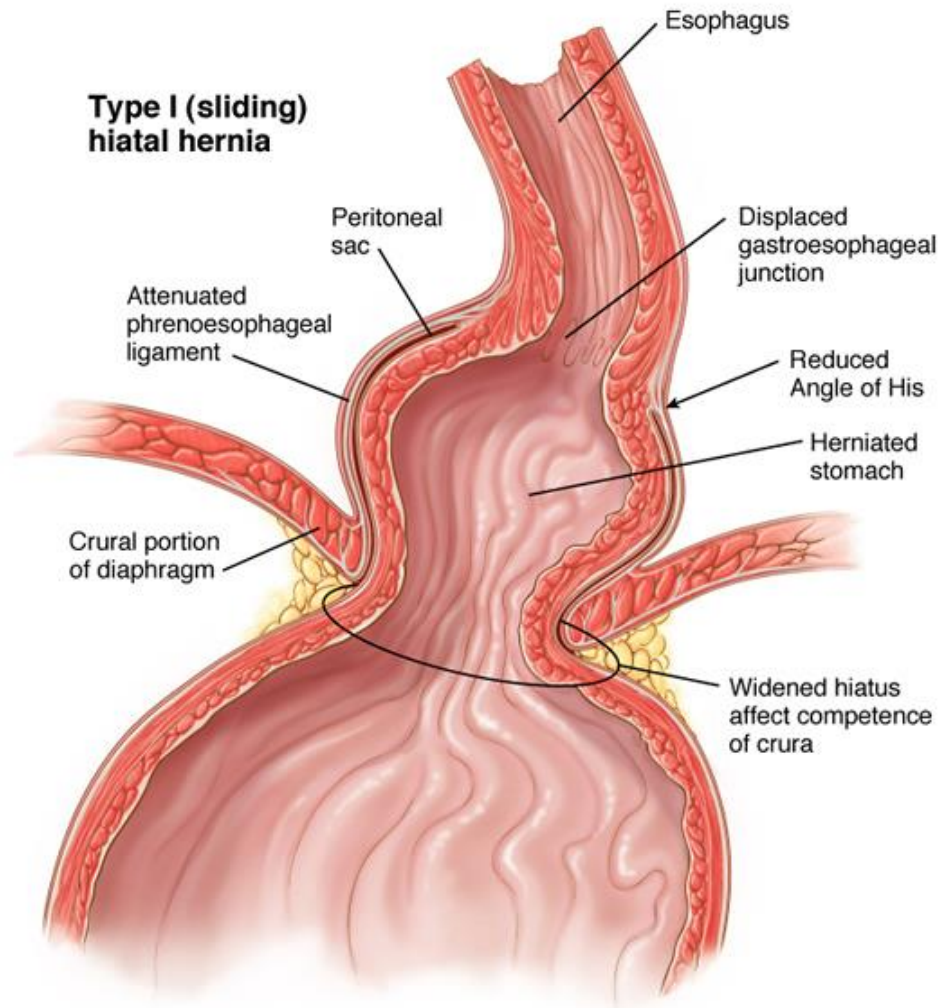
*Clin Gastroenterol Hepatol.* 2017 Aug;15(8):1162-1172



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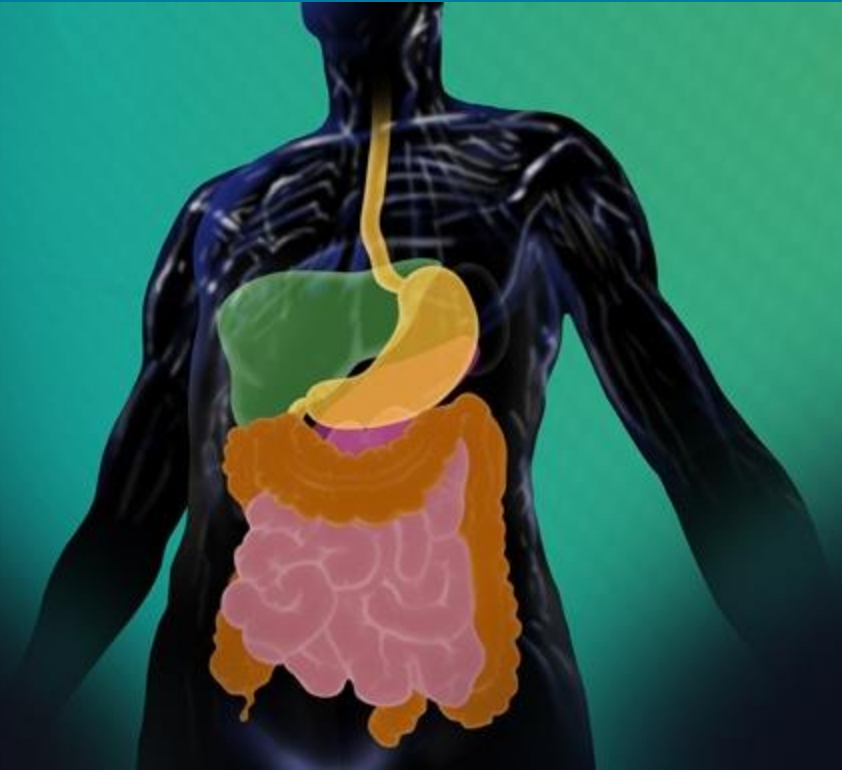
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# What is a hiatal hernia?





# Management of GERD



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# Lifestyle modification

- Evidence for improvement is mostly anecdotal
- Weight loss and stopping smoking the only *proven* ways to reduce heartburn symptoms
- Weight reduction
  - Decrease in BMI of as little as 3.5 lbs/in<sup>2</sup> could result in a 40% decrease in symptom frequency
  - Differential effects of bariatric surgery based on type
    - Roux-en-Y (↓ reflux)
    - Sleeve gastrectomy (↑ reflux)
- Avoid late meals/raise head of bed (most reflux in daytime)
  - Only makes sense for nocturnal symptoms
- Trigger foods are *not* the cause of chronic GERD



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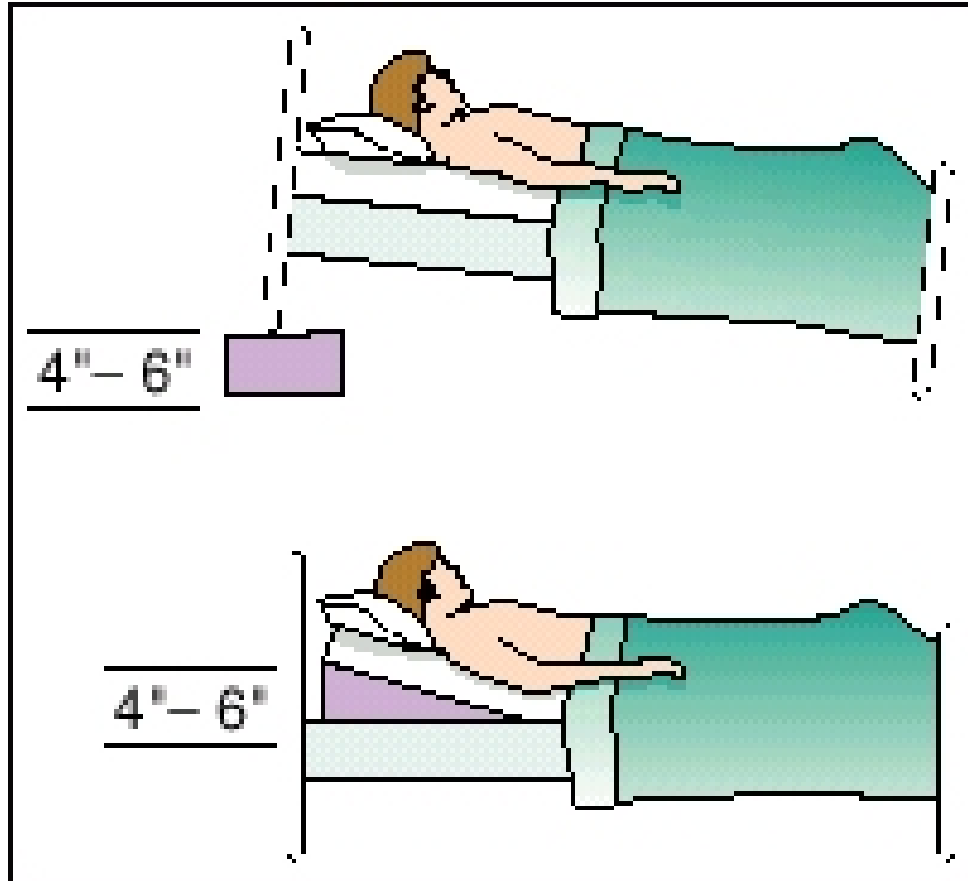
*N Engl J Med.* 2006 Jun 1;354(22):2340-8.

*Clin Gastroenterol Hepatol.* 2016 Feb;14(2):175-82.e1-3.

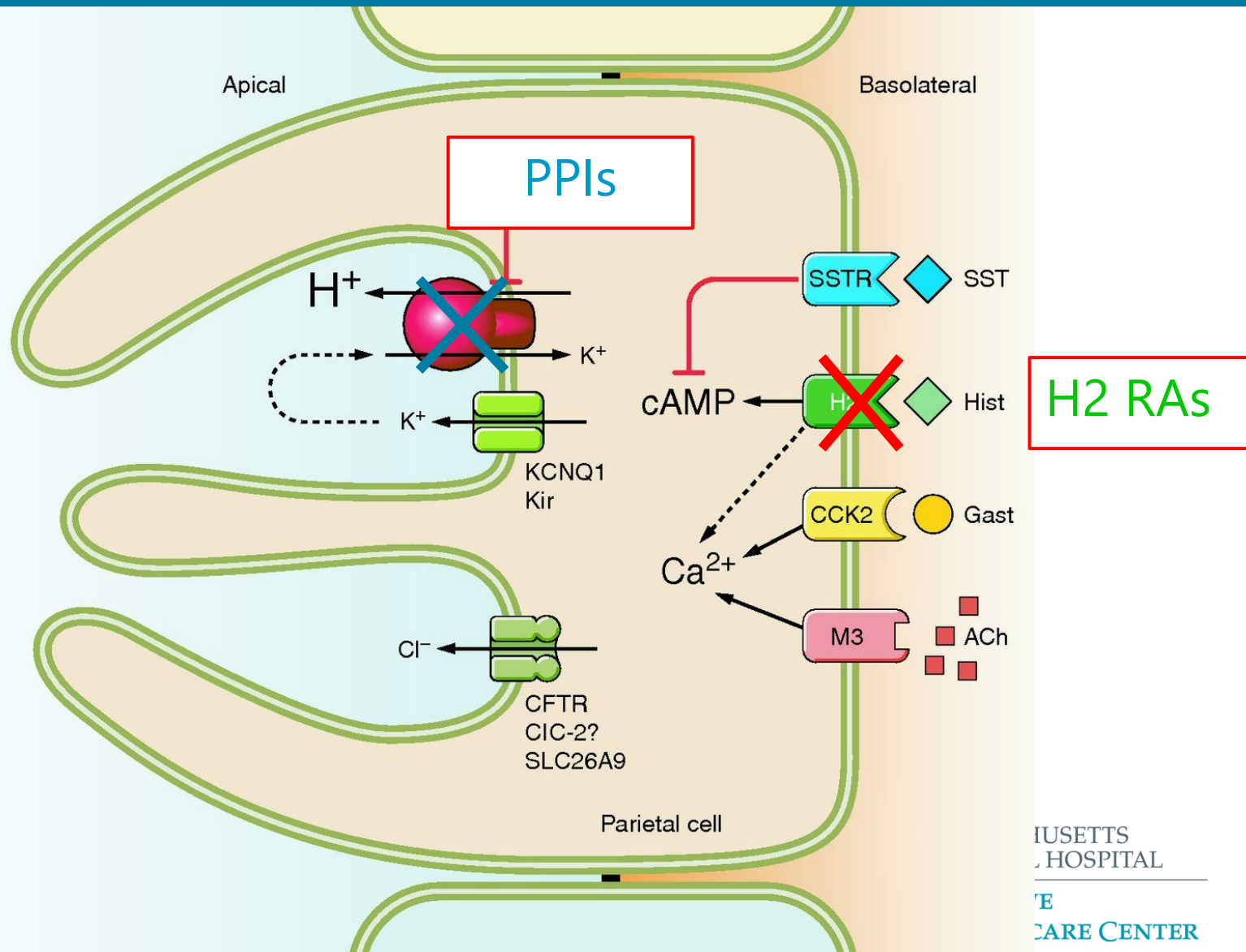


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# H2 receptor antagonists vs. PPIs



# H2 receptor antagonists vs. proton pump inhibitors



- H2 receptor antagonists
  - Ranitidine, cimetidine, famotidine (generic, OTC)
  - Rapid action
  - Not influenced by meals
  - Weaker than PPI
  - Tachyphylaxis
- Proton pump inhibitors
  - Omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole
  - Needs to be taken prior to a meal
  - Even bid acid suppression is not complete



# Proton pump inhibitor failure: what next?

- Most PPIs are basically the same (i.e. the most expensive drug is not going to be the difference maker)

**Table 1.** Potency of PPIs Based on OE

Drug at lowest available dosage	OE
Pantoprazole 20 mg	4.5 mg
Lansoprazole 15 mg	13.5 mg
Omeprazole 20 mg	20 mg
Esomeprazole 20 mg	32 mg
Rabeprazole 20 mg	36 mg

NOTE. PPIs are listed in order of increasing potency.<sup>17</sup>  
OE, omeprazole equivalent; PPIs, proton pump inhibitors.



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*Clin Gastroenterol Hepatol.* 2018 Jun;16(6):800-808.e7.



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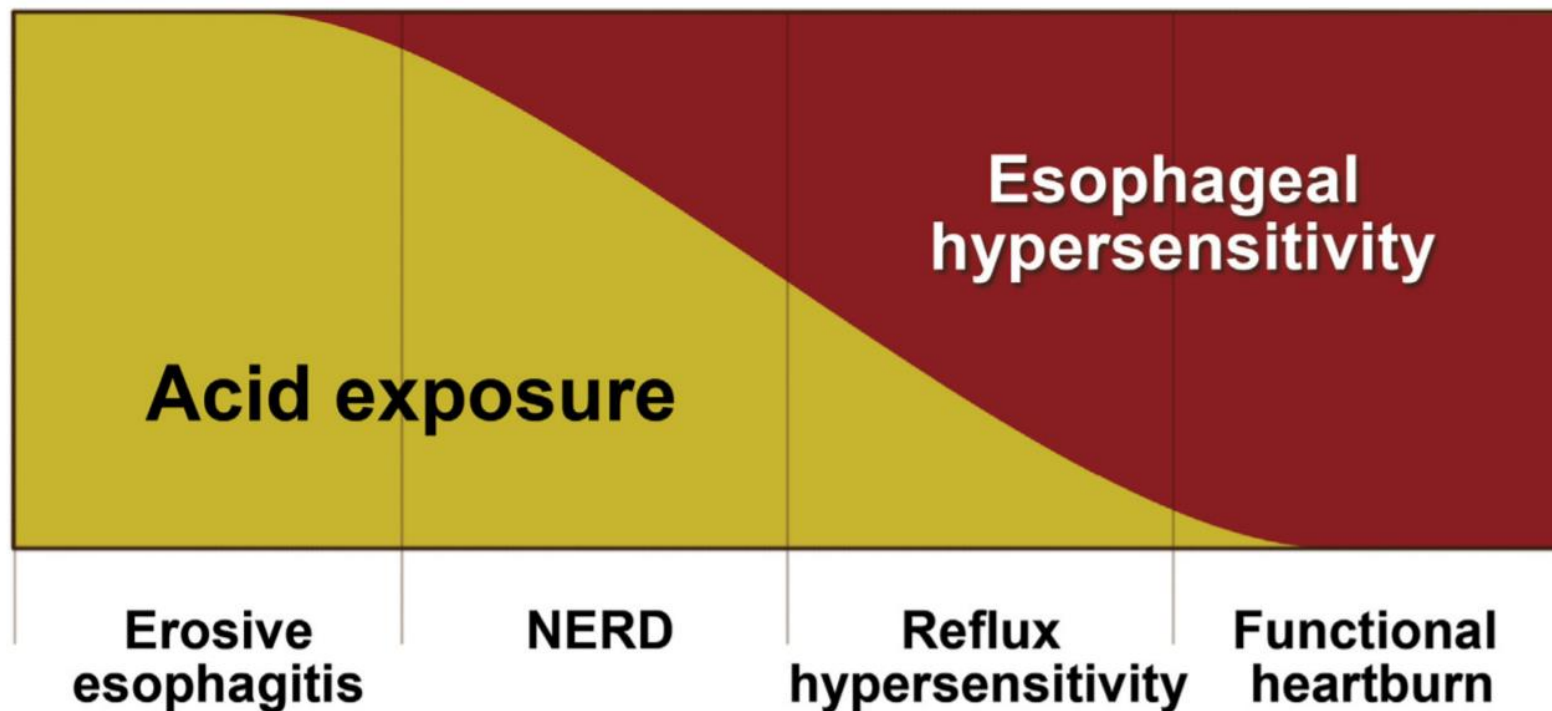
# Proton pump inhibitor failure: what next?

- Dosing time
  - Essential that PPIs are taken at least 30 minutes before a meal
  - Ensure that PPI dosing times correspond to symptom times
- Insufficient dosing
  - Don't be afraid to push dose twice daily dosing as a diagnostic/therapeutic trial...but don't forget to d/c if no improvement
- Visceral hypersensitivity or functional heartburn
  - Exquisite sensitivity to normal amount of acidic reflux
  - Sensitivity to non-acid reflux (after neutralization by PPIs)





# Proton pump inhibitor failure: what next?

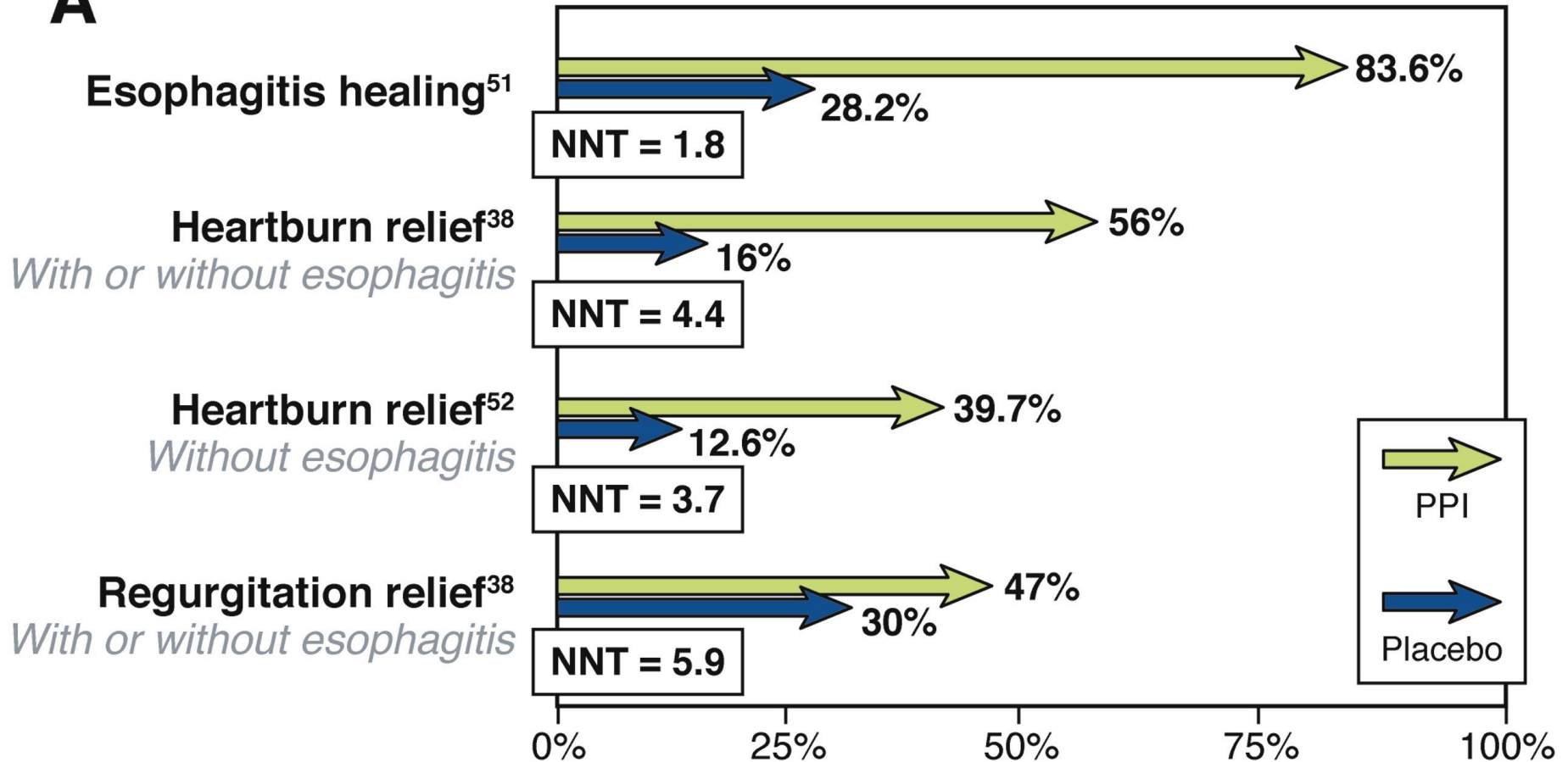


- Alternative diagnosis? (more on that later)
- Anti-reflux surgery (only for people who respond to PPIs)



# Diminishing effect with less classic GERD symptoms

**A**



*Clin Gastroenterol Hepatol.* 2020 Apr;18(4):767-776.



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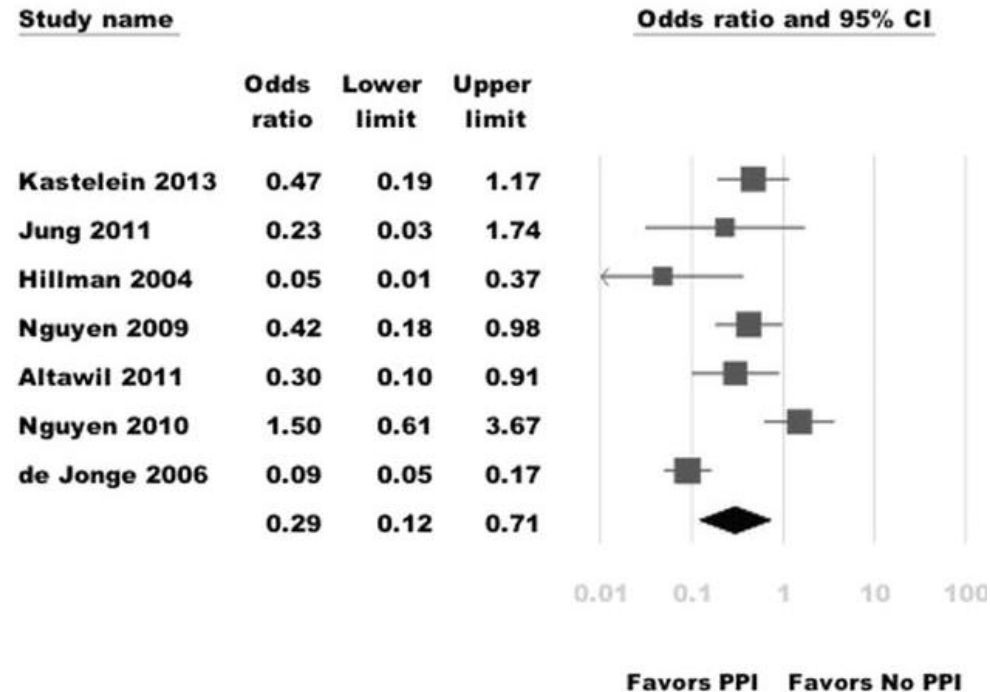


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# Long-term treatment

- Most true GERD patients require long-term treatment
- GERD + esophagitis?
  - *Probably needs lifelong treatment*
- GERD w/ Barrett's esophagus?
  - *Likely benefit to lifelong treatment*
- GERD without esophagitis?
  - *Consider on-demand PPI therapy (!?!)*



*Am J Gastroenterol.* 2016 Jan;111(1):30-50.

Shaheen NJ, Falk GW, *et al.* *Am J Gastroenterol.* 2022 Apr 1;117(4):559-587.

Figure: Singh S, Gard SK, *et al.* *Gut.* 2014 Aug;63(8):1229-37.



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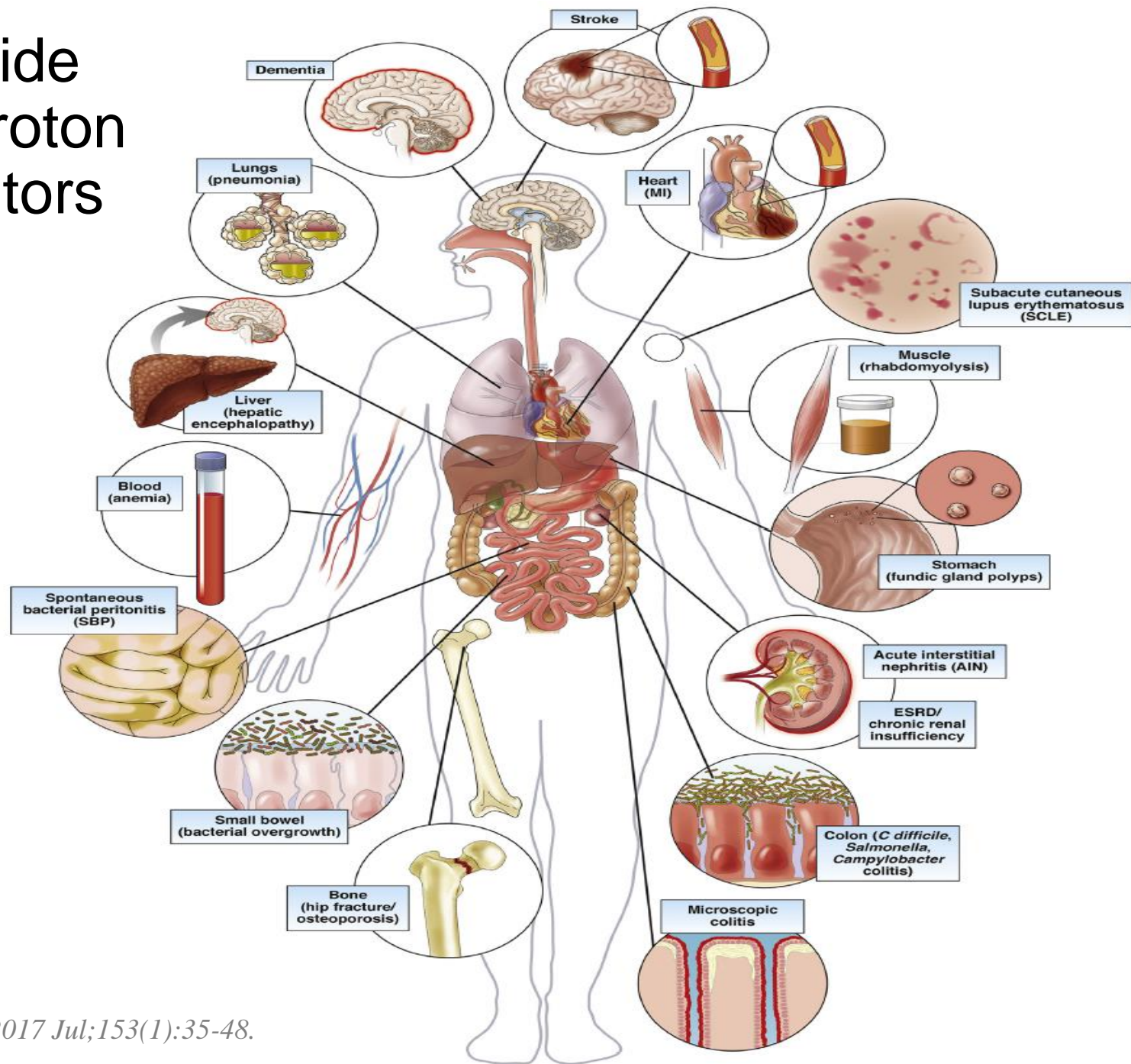
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# Mitigating the risks of long-term PPI therapy

- Use lowest dose that is still effective at symptom control
  - Many patients inappropriately maintained on PPIs who don't need them
- Beware rebound acid hypersecretion w/ PPI stoppage and have strategy in place
  - Consider 1 week overlap with H2RA
- Know the risks of long-term PPI use but don't scare patients away who truly need them



# Proposed side effects of proton pump inhibitors





# Putting risk in perspective with PPIs

- Absolute risk is actually quite small for all associations between PPIs and adverse effects
- One lottery ticket vs. two lottery tickets analogy

**Table 3.** Absolute and RRs for Adverse Effects Associated With Long-Term PPIs

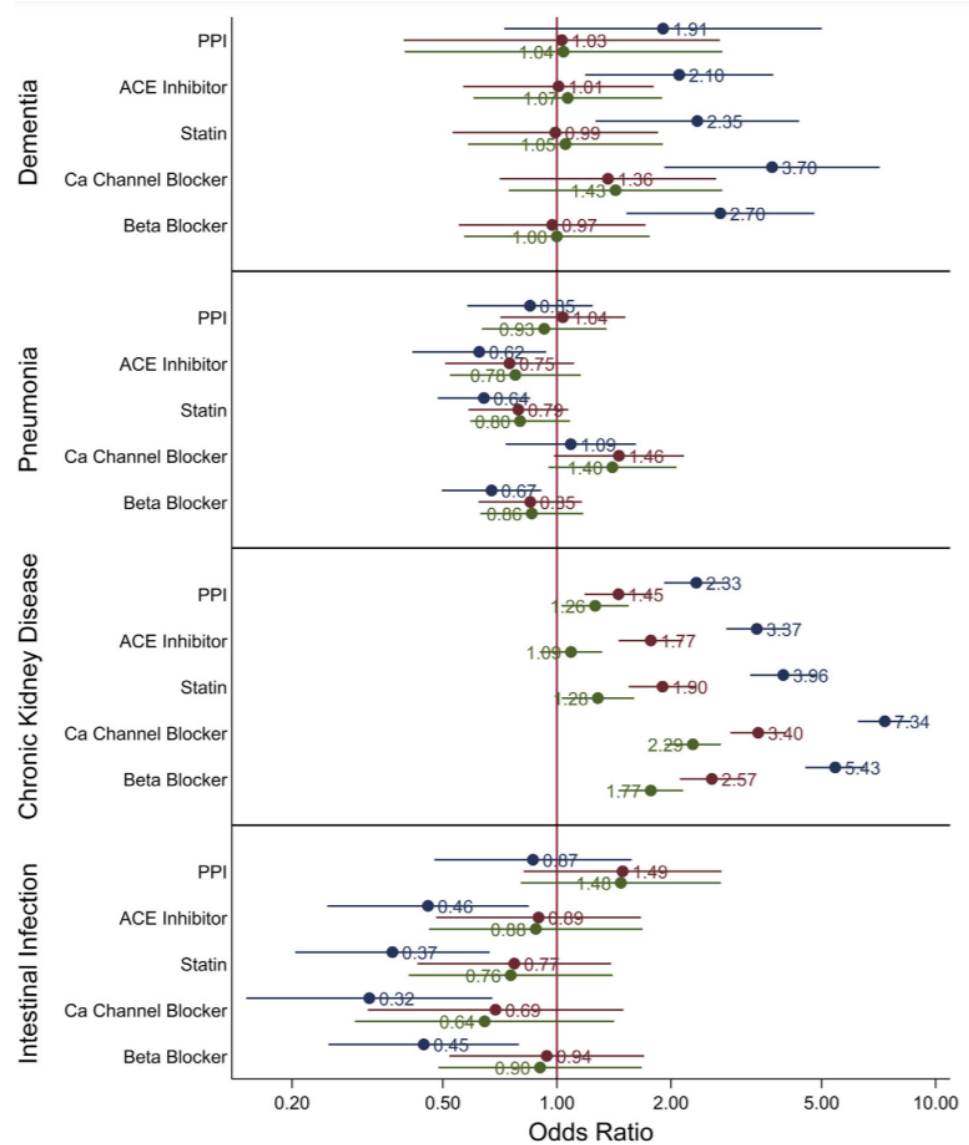
Potential Adverse Effect	Relative Risk	Reference for Risk Estimate	Reference for Incidence Estimate	Absolute Excess Risk
Chronic kidney disease <sup>a</sup>	10% to 20% increase	Lazarus et al <sup>48</sup>	Lazarus et al <sup>48</sup>	0.1% to 0.3% per patient/y
Dementia <sup>b</sup>	4% to 80% increase	Haenisch et al <sup>90</sup>	Haenisch et al <sup>90</sup>	.07% to 1.5% per patient/y
Bone fracture <sup>c</sup>	30% to 4-fold increase	Yang et al <sup>27</sup>	Yang et al <sup>27</sup>	0.1% to 0.5% per patient/y
Myocardial infarction	No association in RCTs	—	—	—
Small intestinal bacterial overgrowth	2-fold to 8-fold increase	Lo et al <sup>91</sup>	None available	Unable to calculate
<i>Campylobacter</i> or <i>Salmonella</i> infection	2-fold to 6-fold increase	Bavishi et al <sup>26</sup>	Crim et al <sup>92</sup>	.03% to 0.2% per patient/y
Spontaneous bacterial peritonitis <sup>d</sup>	50% to 3-fold increase	Xu et al <sup>93</sup>	Fernandez et al <sup>94</sup>	3% to 16% per patient/y
<i>Clostridium difficile</i> infection <sup>e</sup>	No risk to 3-fold increase	Furuya et al <sup>95</sup>	Lessa et al <sup>96</sup>	0% to .09% per patient/y
Pneumonia	No association in RCTs	—	—	—
Micronutrient deficiencies <sup>f</sup>	60% to 70% increase	Lam et al <sup>97</sup>	Bailey et al <sup>98</sup>	0.3% to 0.4% per patient/y
Gastrointestinal malignancies	No association in RCTs	—	—	—





# Interpreting reported risks of PPIs: the effect of residual confounding

- Unadjusted
- Adjusted for Demographics
- Adjusted for Demographics & Comorbidities



# Finally, some prospective data

## **Safety of Proton Pump Inhibitors Based on a Large, Multi-Year, Randomized Trial of Patients Receiving Rivaroxaban or Aspirin**

- Large, multi-year RCT of people with CVD/PAD in trial of rivaroxaban, ASA, Pantoprazole
- Followed over 3 years with no increased risk of:
  - Pneumonia
  - Fractures, gastric atrophy
  - Chronic kidney disease,
  - Dementia
  - Cardiovascular disease
  - All-cause mortality

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*Gastroenterology*. 2019 May 29. pii: S0016-5085(19)40974-8.



## Part II: Irritable Bowel Syndrome



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# Rome IV now has clinical criteria

Recurrent  
abdominal pain

>1 day/week in last 3 months

+ 2 or more of

Related to  
defecation

Associated with  
change in  
frequency of stool

Associated with  
change in form of  
stool

*Criteria filled for the last 8 weeks (formal definition requires 6 months)*

- **Pain** is king; “discomfort” no longer part of the IBS lexicon
- Higher frequency of pain than previously
- Association *not* improvement with defecation



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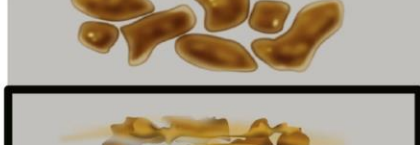




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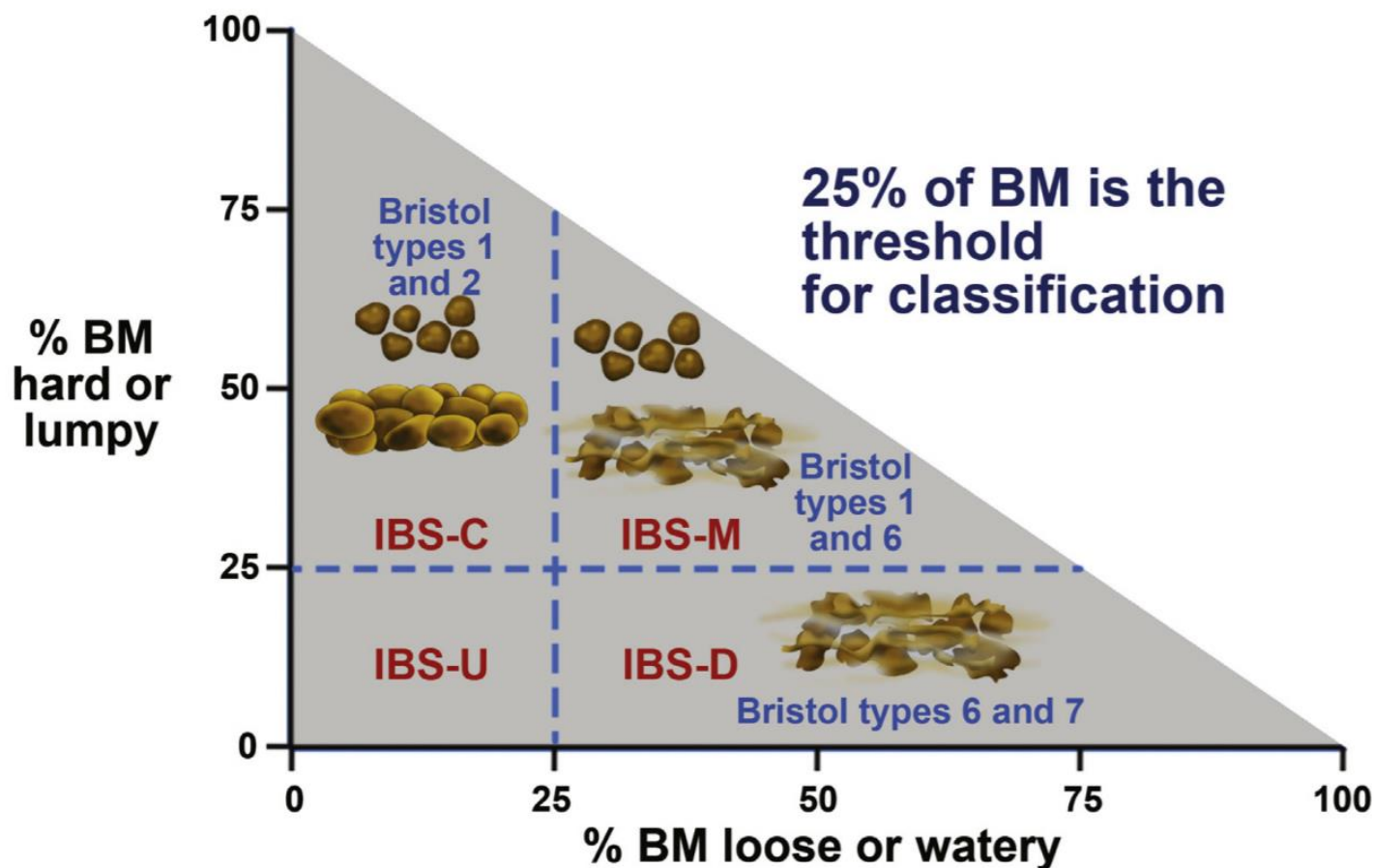
Drossman D, Tack J. *Gastroenterology*. 2022 Mar;162(3):675-679.

# Stool form as a surrogate for colonic transit time

Type 1		<b>Separate hard lumps, like nuts (hard to pass)</b>
Type 2		<b>Sausage-shaped but lumpy</b>
Type 3		<b>Like a sausage but with cracks on the surface</b>
Type 4		<b>Like a sausage or snake, smooth and soft</b>
Type 5		<b>Soft blobs with clear-cut edges</b>
Type 6		<b>Fluffy pieces with ragged edges, a mushy stool</b>
Type 7		<b>Watery, no solid pieces, entirely liquid</b>



# Stool form defines IBS subtype



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Drossman D, Hasler WL. *Gastroenterology*. 2016; 150:1393-1407.



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# Diagnostic testing in IBS



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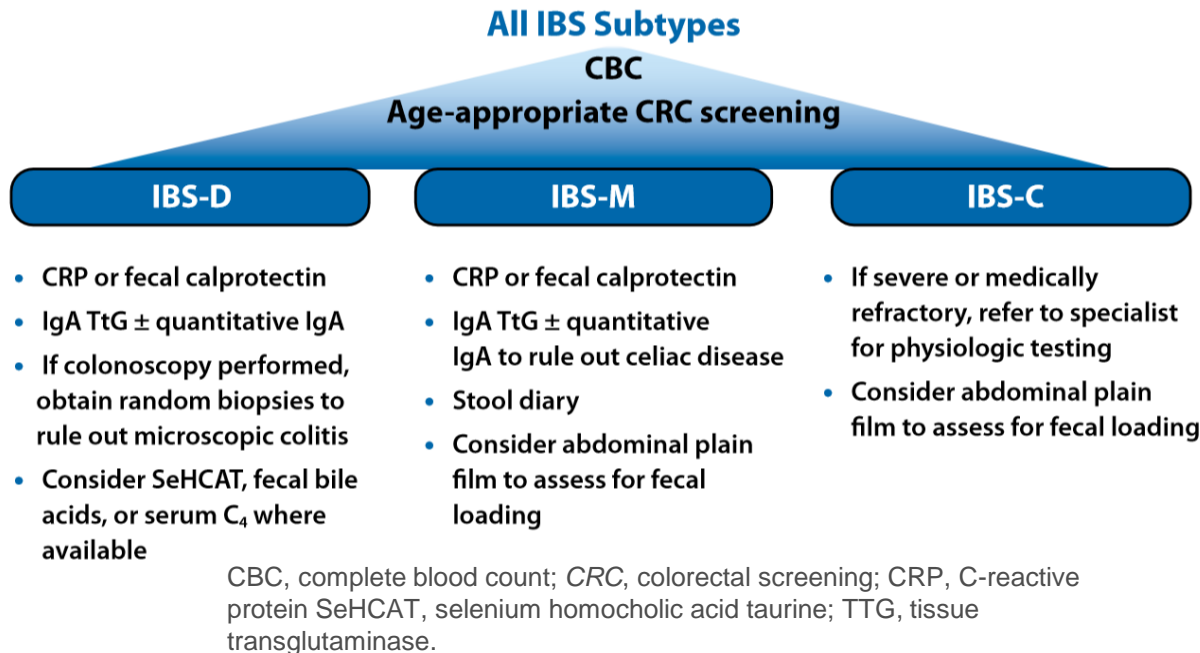


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# Diagnostic testing for patients with suspected IBS and no concerning\* features



## \* Alarm features

- Age ≥50 years old
- Blood in stools
- Iron-deficiency anemia
- Nocturnal symptoms
- Unintentional weight loss
- Change in symptoms
- Palpable abdominal mass or lymphadenopathy
- Family history of organic GI disease

- Latest guidelines on testing:
  - Avoid stool pathogen testing in IBS
  - Avoid food allergy testing in IBS

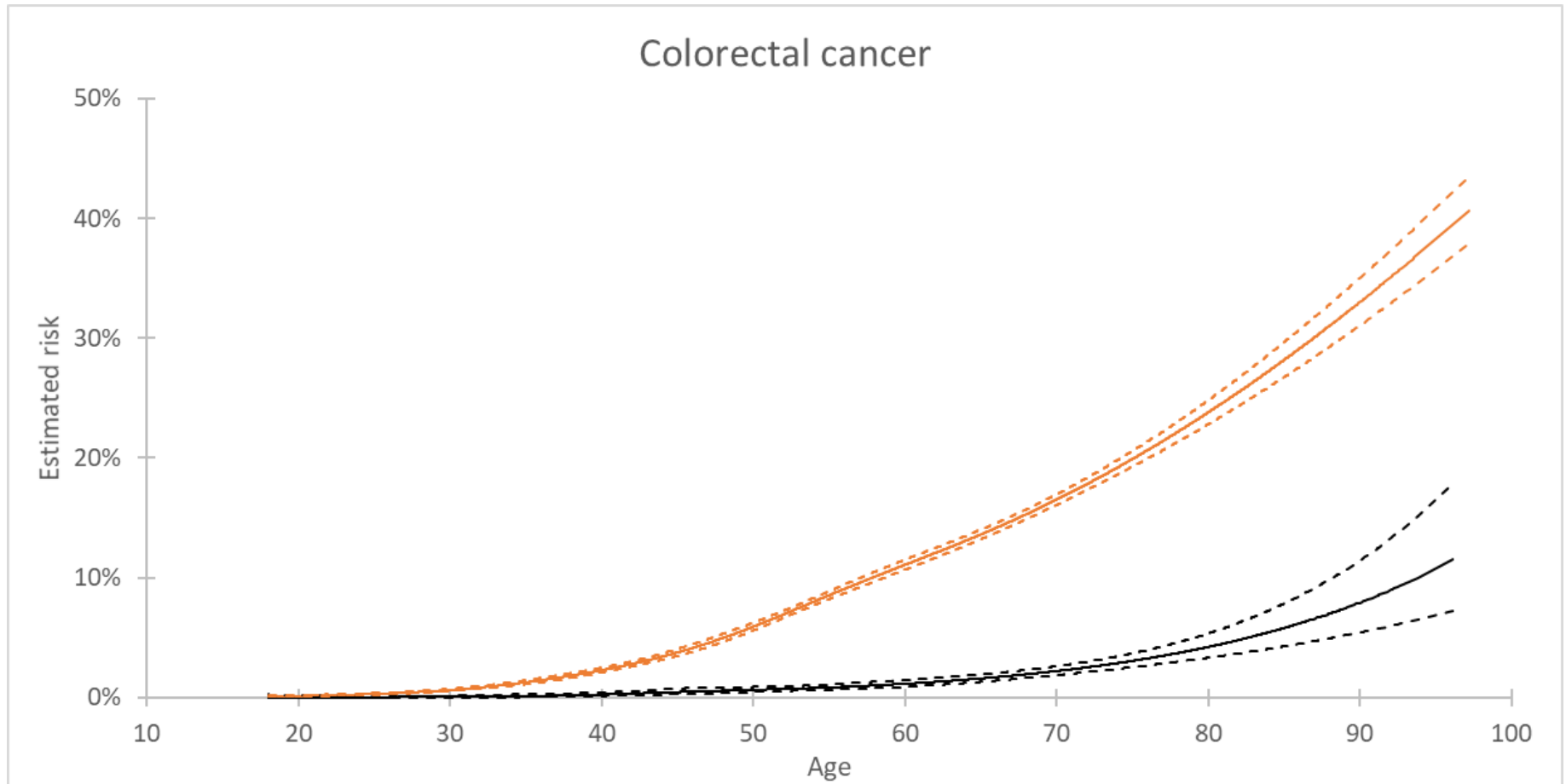
Adapted from: Schdenfeld, PS. *Gastroenterol Hepatol (N Y)*. 2016 Aug;12(8 Suppl 3):1-11.  
Lacy BE, Pimentel M, et al. *Am J Gastroenterol*. 2021 Jan 1;116(1):17-44.



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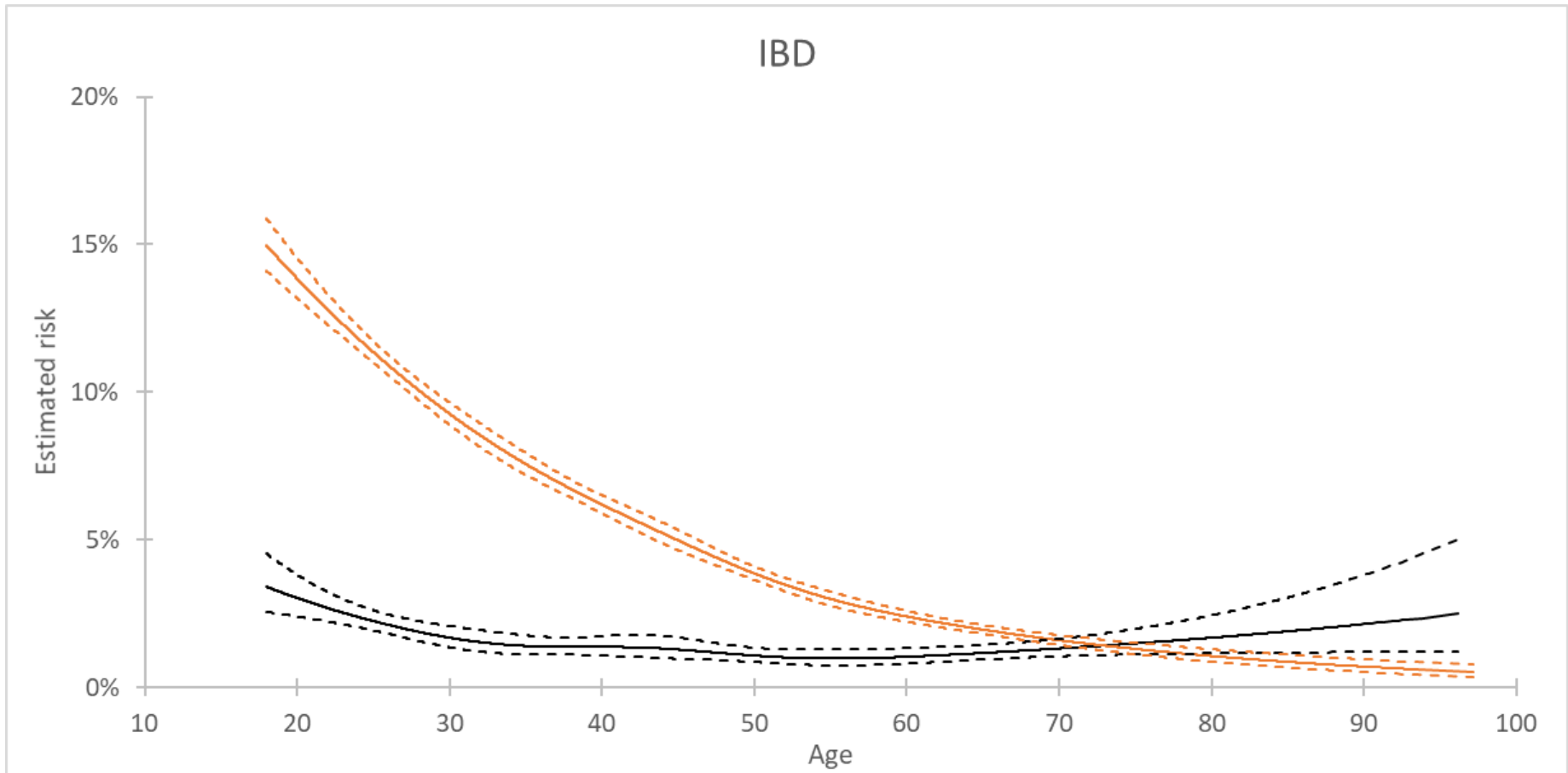
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# Why colonoscopy is *not* recommended in IBS without alarm symptoms



IBS		Comparators	
—	Predicted risk	—	Predicted risk
- - -	95% CI	- - -	95% CI

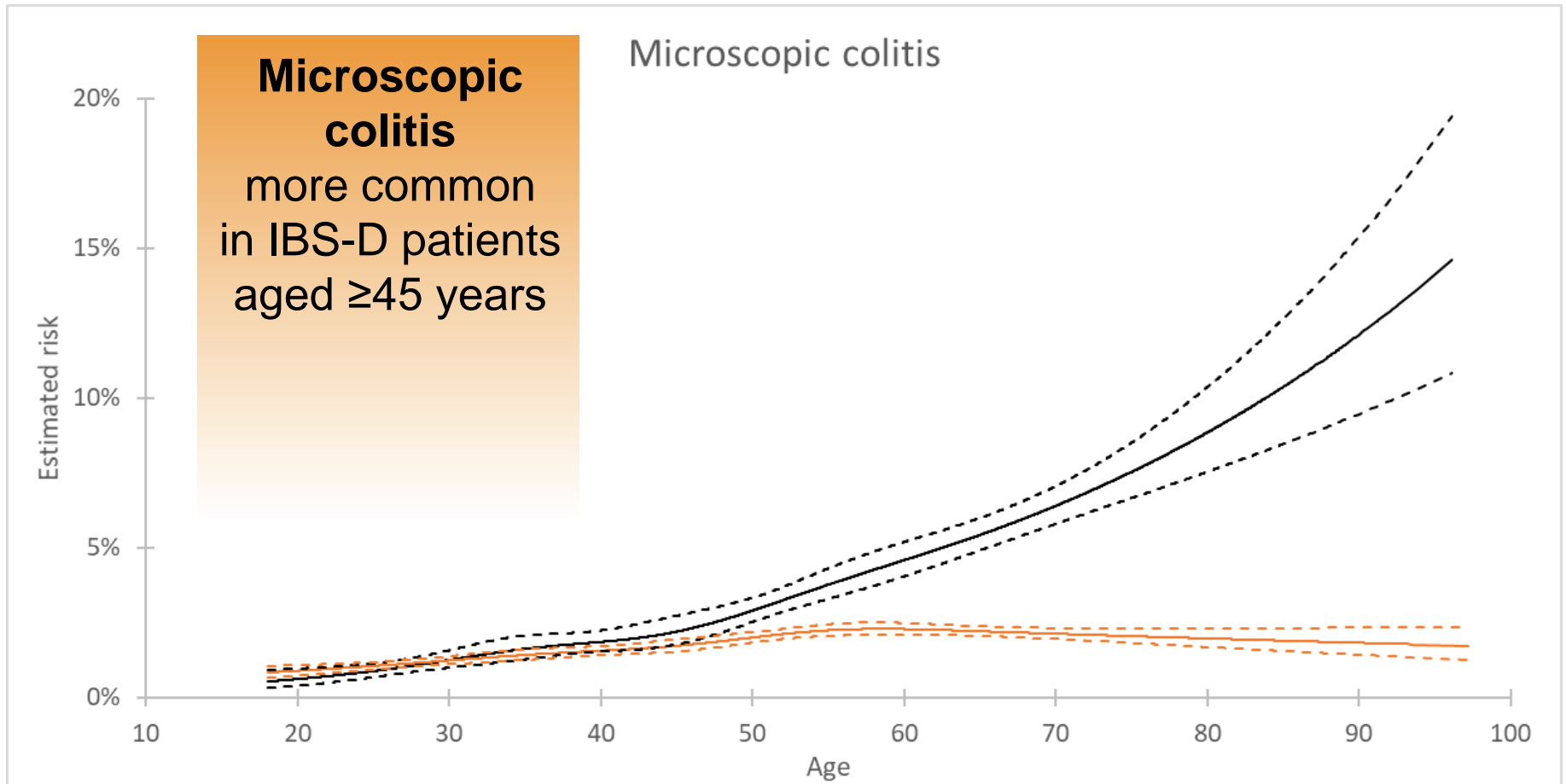
# Why colonoscopy is *not* recommended in IBS without alarm symptoms



**IBS**  
— Predicted risk  
- - - 95% CI

**Comparators**  
— Predicted risk  
- - - 95% CI

# Why colonoscopy is *not* recommended in IBS without alarm symptoms...but wait

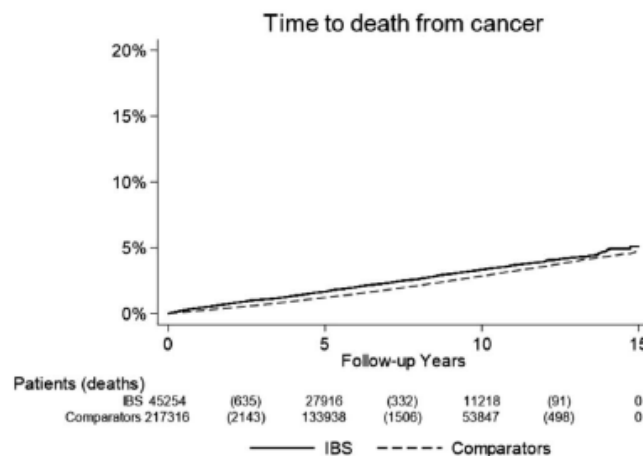
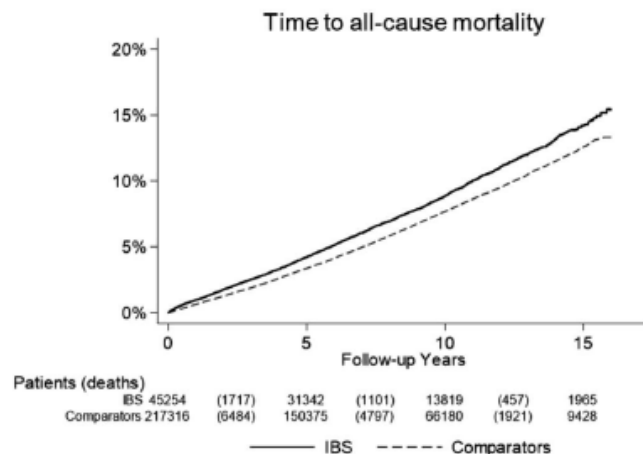


**IBS**  
— Predicted risk  
- - - 95% CI

**Comparators**  
— Predicted risk  
- - - 95% CI

# No, IBS will not kill you

- Mortality concern is a major driver of care seeking in patients with IBS
- In this nationwide cohort of >45,000 individuals: no association between IBS and mortality
- No increased risk of mortality from cancer either
- Clinicians should spend more time on patient education and effective treatment approaches



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K Staller, O Olén, *et al.* *Am J Gastroenterol.* 2020 Feb 28 (online ahead of print).



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# Dietary treatments for IBS



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# Fiber!

- Vague advice to increase fiber is not always helpful
- Multiple studies indicate that soluble fiber (*not* insoluble fiber) is most beneficial
  - Bijkerk *et al* randomly allocated patients to psyllium, bran, or placebo for 12 weeks
  - By the second month, more patients were responding in the psyllium group than in bran or placebo groups
- Beware of FODMAPs (more soon)

# Fiber!

- Vague advice to increase fiber is not always helpful

	<b>BRAND NAME</b>	<b>DOSE</b>
Psyllium	Metamucil	2.5-30g daily, divided doses
Methylcellulose	Citrucel	500mg, 1-2 tbsp daily-tid
Calcium polycarbophil	FiberCon	1250 mg bid-qid

responding in the psyllium group than in bran or placebo groups

- Fiber supplements are not useful unless combined with increased fluid intake



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*C J Bijkerk, N J de Wit et al, BMJ. 2009;339:b3154.*



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# Patient demand for dietary advice in IBS outstrips the supply of available evidence for providers

- More than 70% of IBS patients believe that food plays a role in their symptoms<sup>1</sup>.
- Self-reported food intolerance in IBS is associated with more severe symptom severity<sup>2</sup>.
- Like it or not, your patients will look to you for dietary guidance
- Evolution of concept of non-celiac gluten (wheat) sensitivity

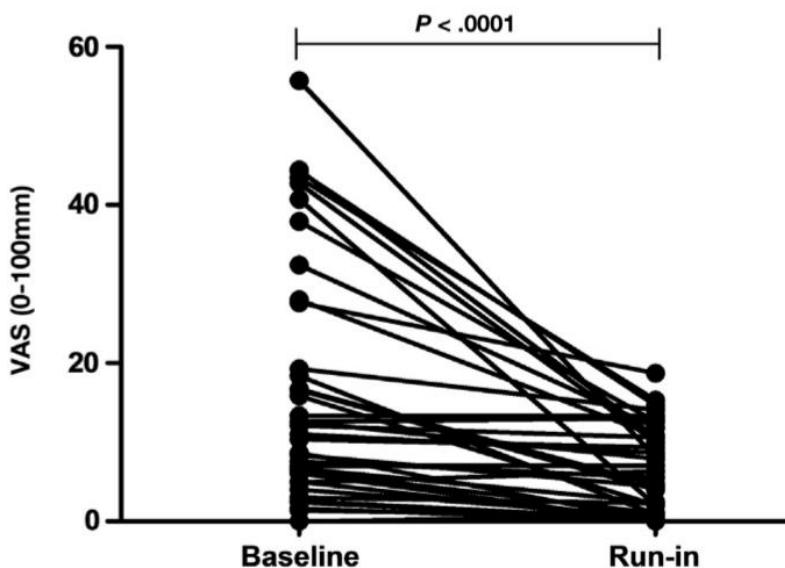


1. *Clin Gastroenterol Hepatol* 2015.

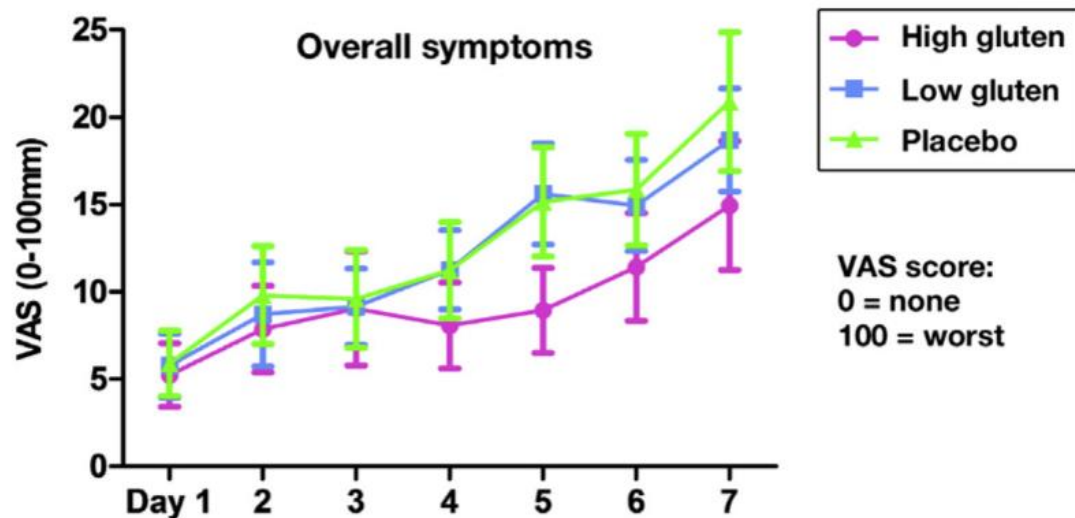
2. *Clin Gastroenterol Hepatol*. 2015 Nov;13(11):1899-906.



# Which diet to choose? Gluten-free or low-FODMAP?



Low FODMAP run-in



Blinded re-introduction of high FODMAP foods



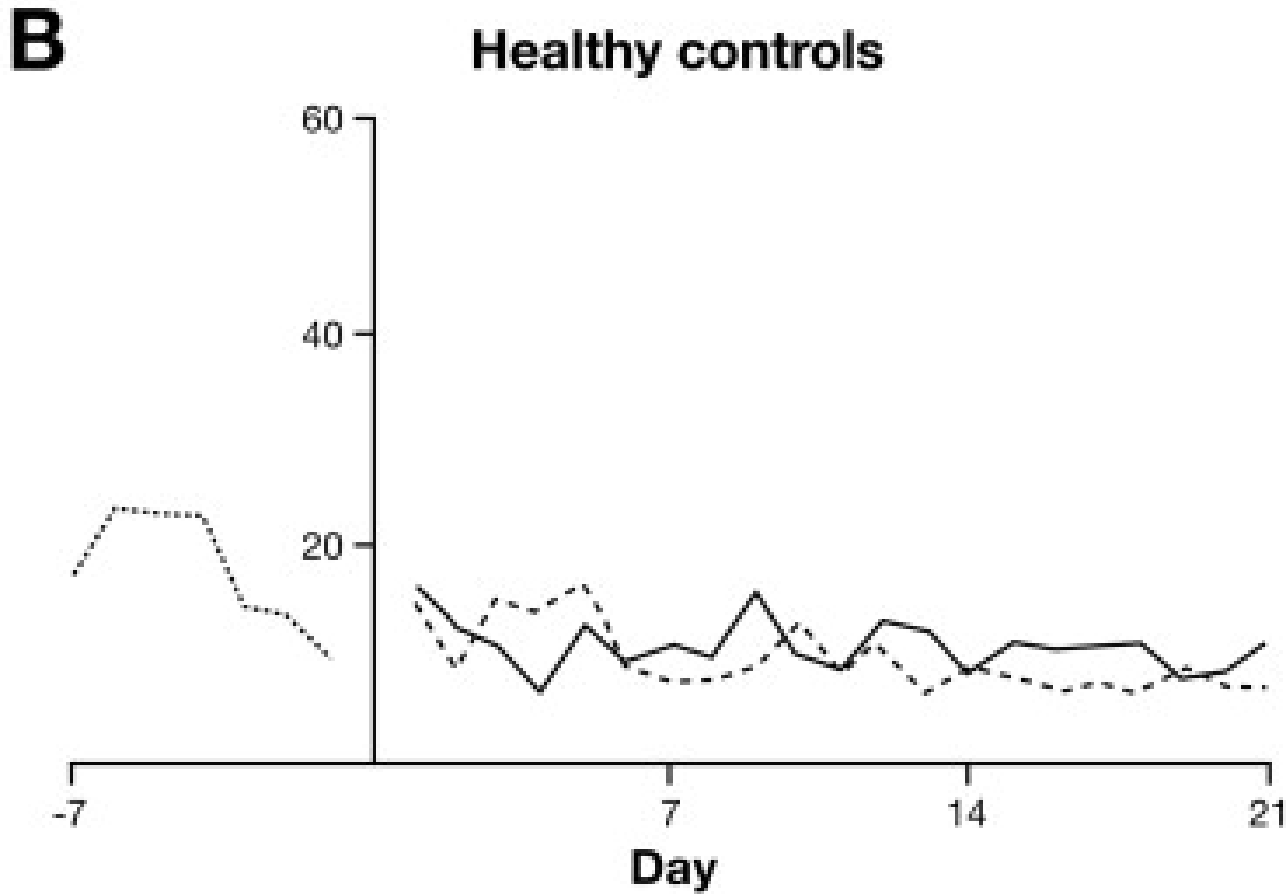
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# Low FODMAP diet has a differential effect on IBS patients compared to healthy controls



*Gastroenterology*. 2014 Jan;146(1):67-75.e5.



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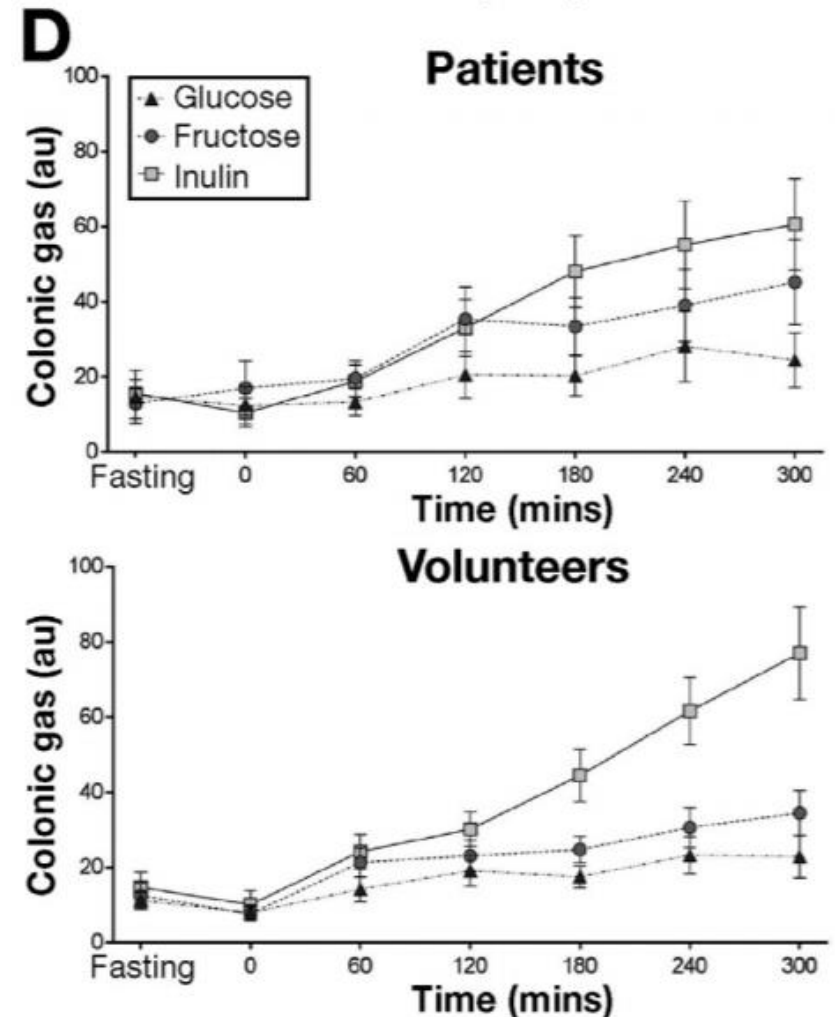
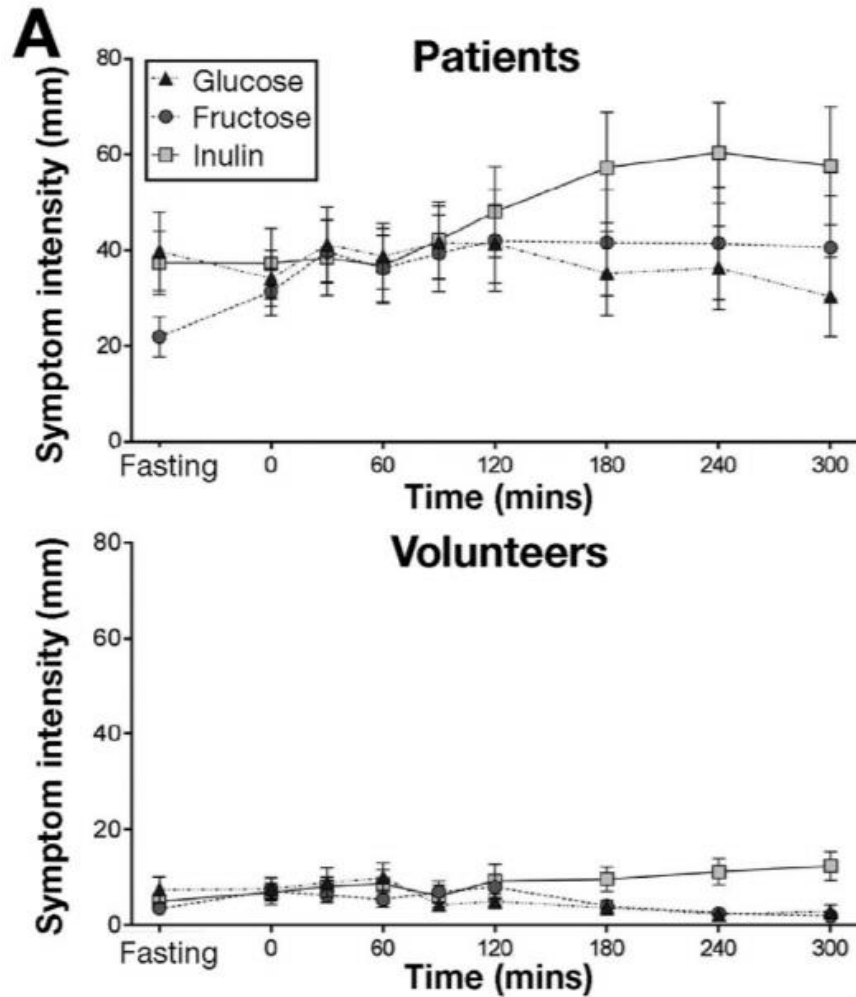
# Caveats of dietary interventions in IBS

- Risk of bias in many dietary trials
- Effect of reintroduction/maintenance phase less certain
- Need a qualified dietician
  - No data on efficacy of printed handouts
  - Monash University app
- Caution in patients w/ disordered eating
  - Can reinforce harmful cognitions/ behaviors
  - Look out for “orthorexia nervosa”
    - Obsessive focus on food choice
    - Food for health > pleasure





# Response to FODMAPs, a matter of nerves?



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*Gastroenterology*. 2017 Jan;152(1):124-133.e2.

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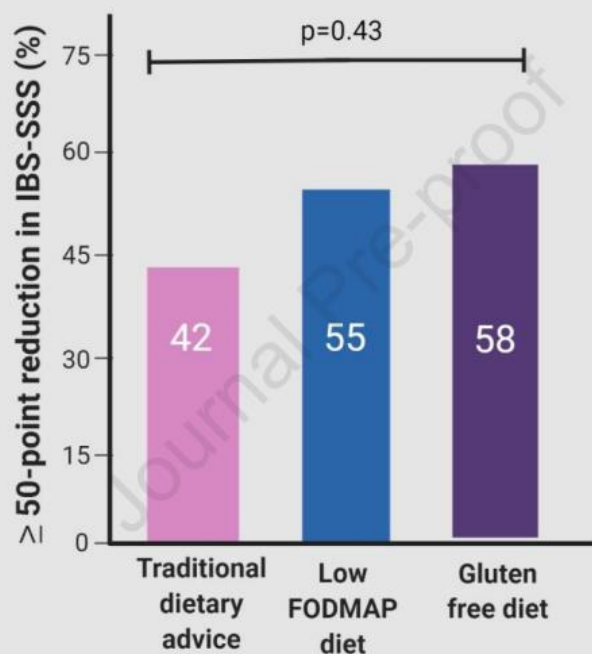
# Maybe any diet will do?

## Efficacy and Acceptability of Dietary Therapies in Non-Constipated IBS

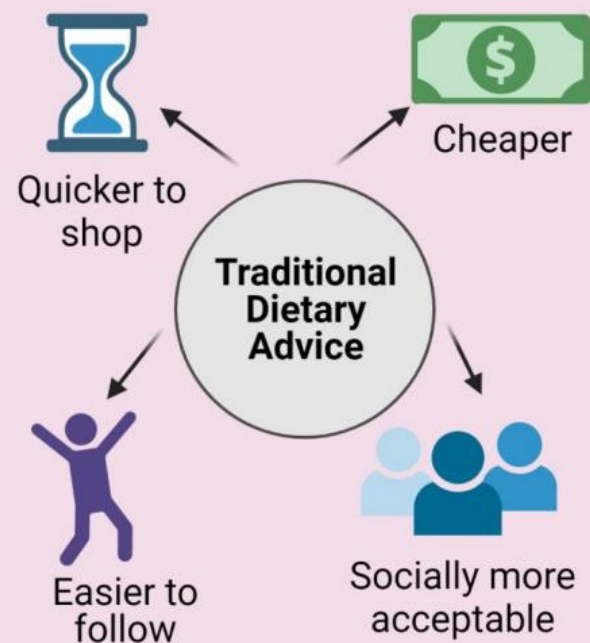
Diet is a key trigger for symptoms in IBS



Comparable efficacy of dietary therapies



Acceptability of Dietary Therapies



All three diets are effective in non-constipated IBS, but traditional dietary advice is the most patient-friendly with regards to cost and convenience

# Questions about probiotics are a reality of taking care of patients with IBS

- Probiotics likely provide some benefit to patients with IBS
- On the whole products containing

In symptomatic children and adults with irritable bowel syndrome, we recommend the use of probiotics only in the context of a clinical trial. *No recommendations, knowledge gap.*

- Any advice to patients limited by poor quality of existing data



# Thinking about pharmacologic treatments for IBS



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# Summary of symptom-specific effects of IBS-D therapies

	Symptom Improvement				
	Global Symptoms	Pain	Bloating	Stool Frequency	Stool Consistency
<b>Alosetron</b>	+	+	+	+	
<b>Antidepressants</b>	+	+			
<b>Eluxadoline</b>	+			+	+
<b>Loperamide</b>				+	+
<b>Antispasmodics</b>	±	+			
<b>Probiotics</b>	+		+		
<b>Rifaximin</b>	+	+	+		+

- Latest guidelines treatment:

- *Global recommended treatments:* peppermint (low evidence), tricyclic antidepressants, low-FODMAP diet, gut-directed psychotherapies
- *IBS-D recommended treatments:* alosetron, eluxadoline, rifaximin, soluble fiber
- *Avoid:* probiotics



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Adapted from ACG Task Force on IBS. *Am J Gastroenterol.* 2014;109(Suppl 1):S2-S26.

Lacy BE, Pimentel M, et al. *Am J Gastroenterol.* 2021 Jan 1;116(1):17-44.

# Summary of symptom-specific effects of IBS-C therapies

	Symptom Improvement				
	Global Symptoms	Pain	Bloating	Stool Frequency	Stool Consistency
Fiber	+			+	+
Laxatives (PEG)				+	+
Lubiprostone	+	+	+		+
Linaclotide	+	+	+	+	+
Plecanatide	+	+	+	+	+
Tenapanor	+	+	+	+	+
Tegaserod (limited)	+	+	+	+	+
Antidepressants	+	+	?		

- Latest guidelines on treatment:
  - *Global recommended treatments*: peppermint (low evidence), tricyclic antidepressants, low-FODMAP diet, gut-directed psychotherapies
  - *IBS-C recommended treatments*: lubiprostone, linaclotide, plecanatide, tegaserod
  - *Avoid*: probiotics, PEG for global IBS-C symptoms

Adapted from ACG Task Force on IBS. *Am J Gastroenterol.* 2014;109(Suppl 1):S2-S26.

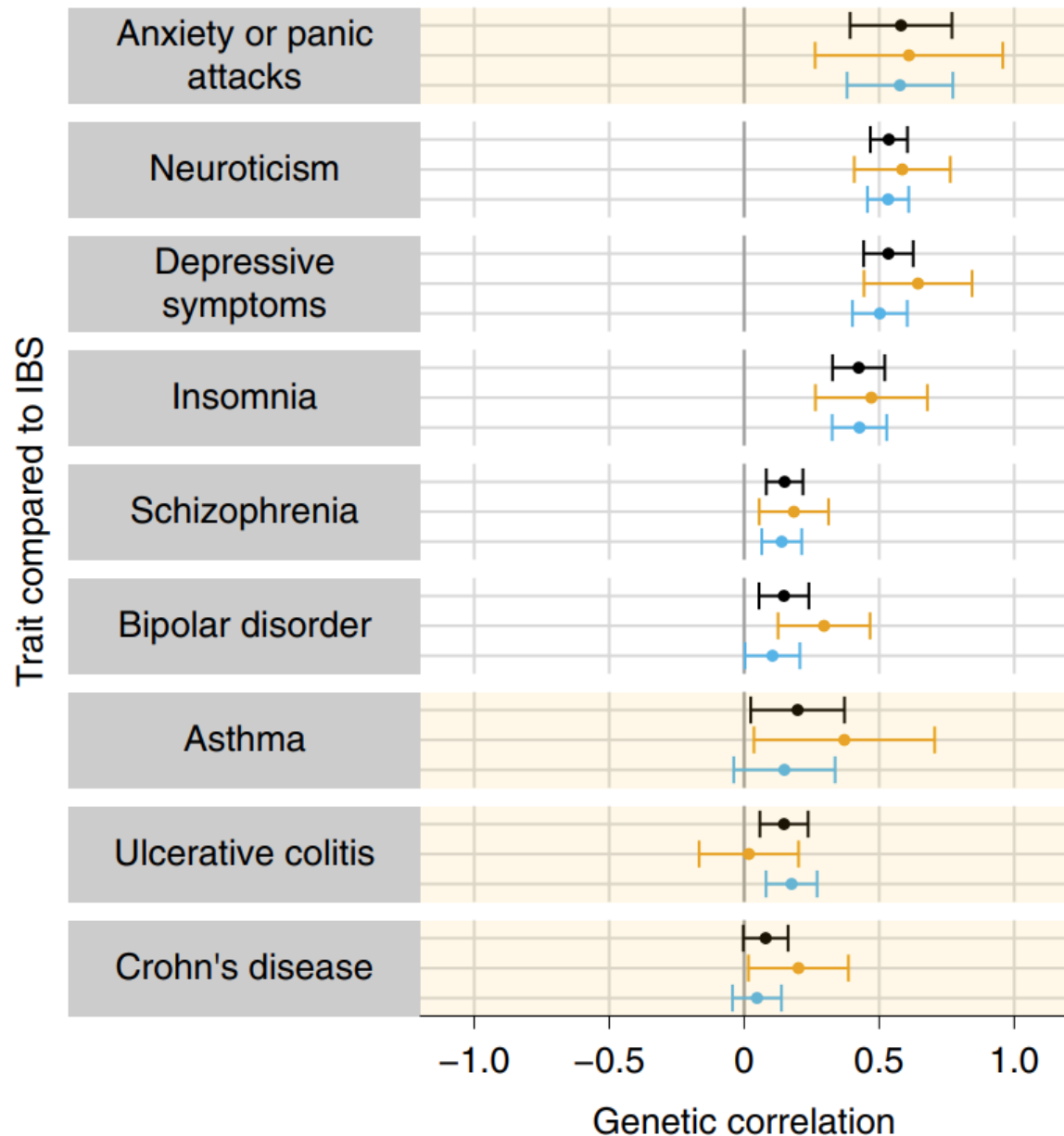
Lacy BE, Pimentel M, et al. *Am J Gastroenterol.* 2021 Jan 1;116(1):17-44.

# IBS and psychological disease: chicken or egg?

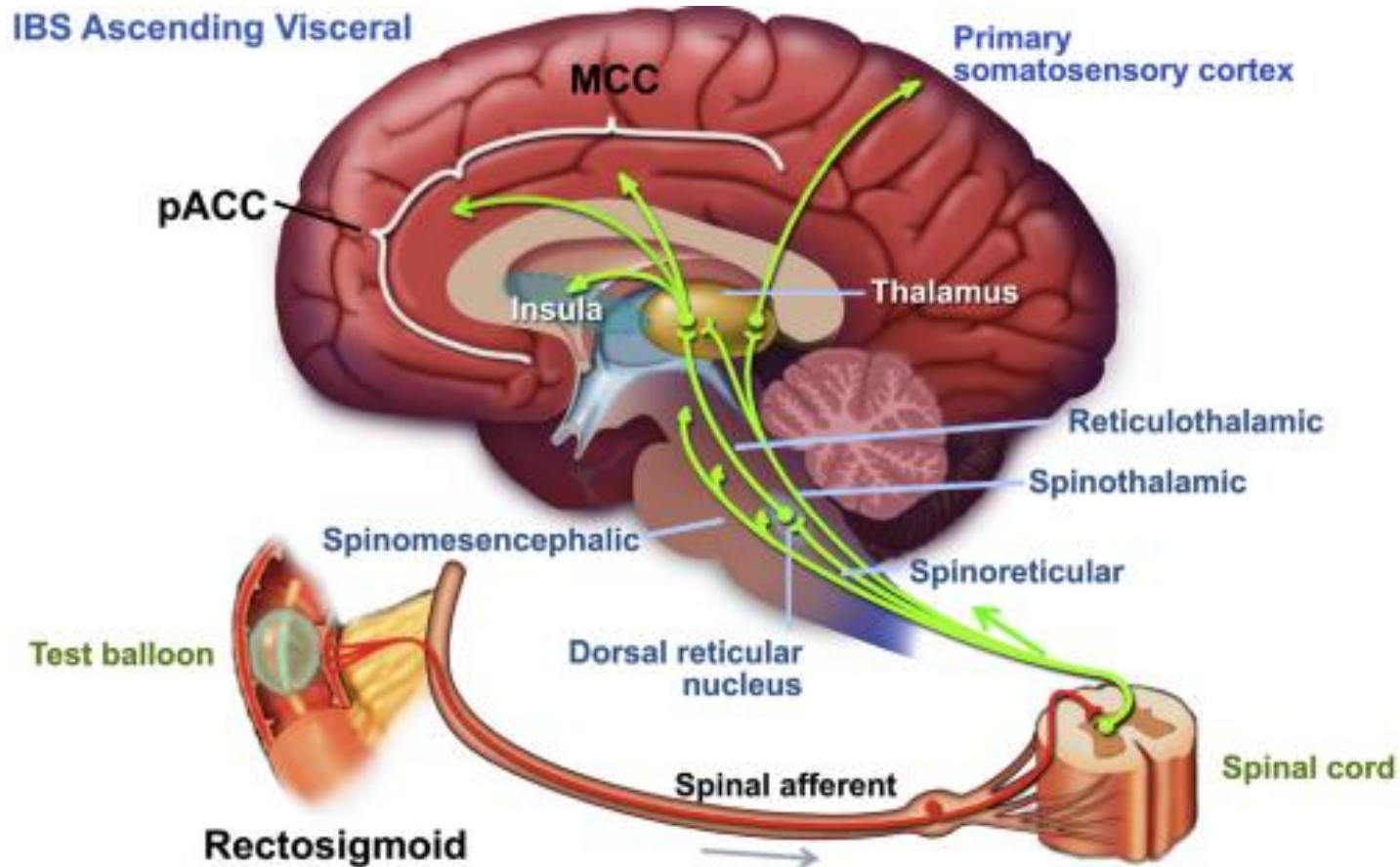
## Genetic correlation between IBS and anxiety

Association remained even after removing those with overlap

Suggests shared etiology rather than one condition causing the other



# How sensory signals from the colon reach consciousness: ascending pathways



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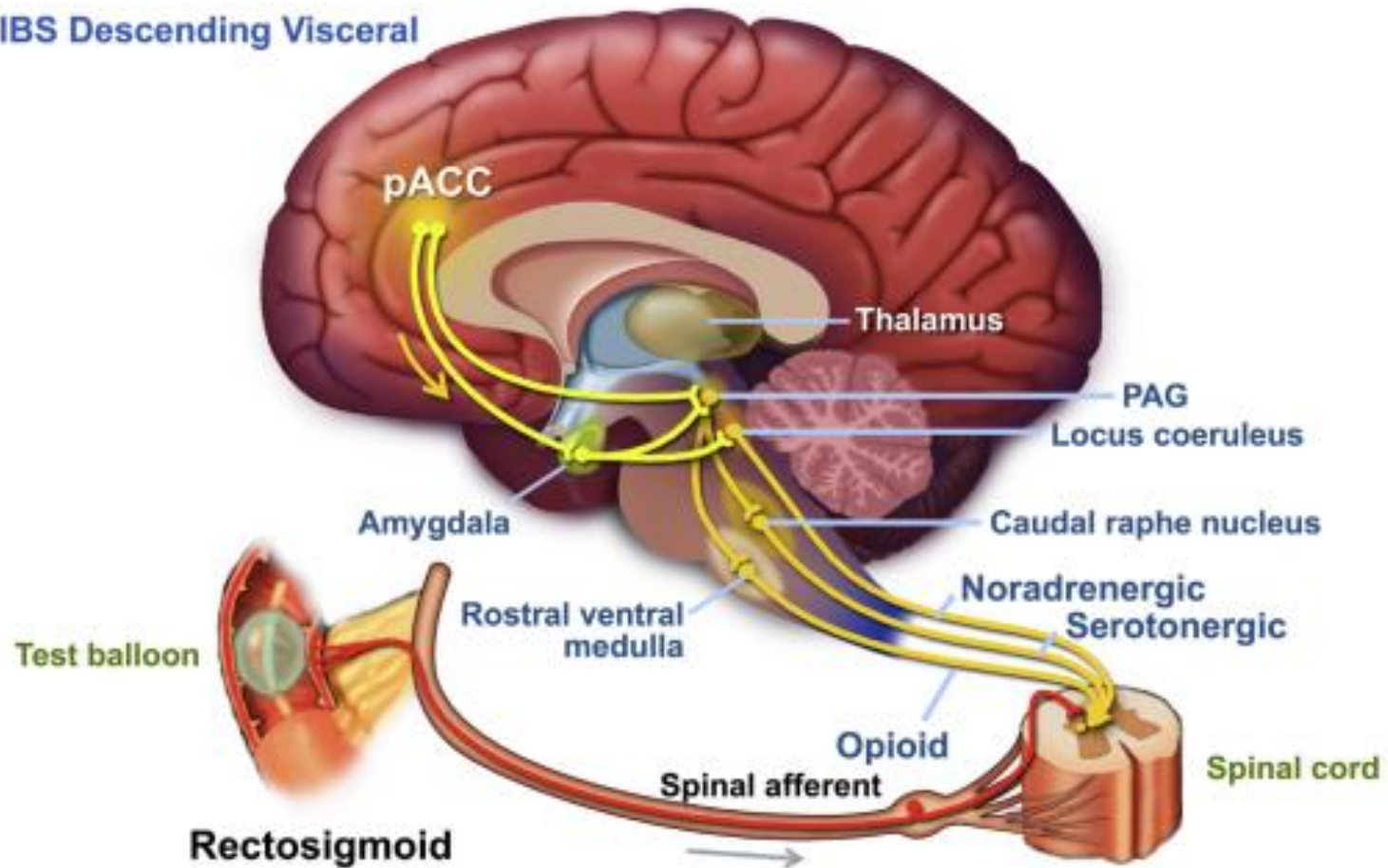
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# How sensory signals from the colon reach consciousness: descending pathways

## IBS Descending Visceral



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# Use of neuromodulators in IBS

- Many patients have improved bowel frequency on laxatives, but bloating/abdominal pain remain
- Neuromodulators reduce global IBS symptoms and pain in IBS patients
- Potential benefits:
  - Reduction in pain/?bloating
  - Treatment of psychological distress and comorbid psychiatric disease
  - Leverage motility effects
  - Long-term treatment may reverse maladaptive brain-gut axis changes



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Sobin WH, Heinrich TW, et al. *Am J Gastroenterol*. 2017 May;112(5):693-702.

Drossman DA, Tack J, et al. *Gastroenterology*. 2018 Mar;154(4):1140-1171.e1.

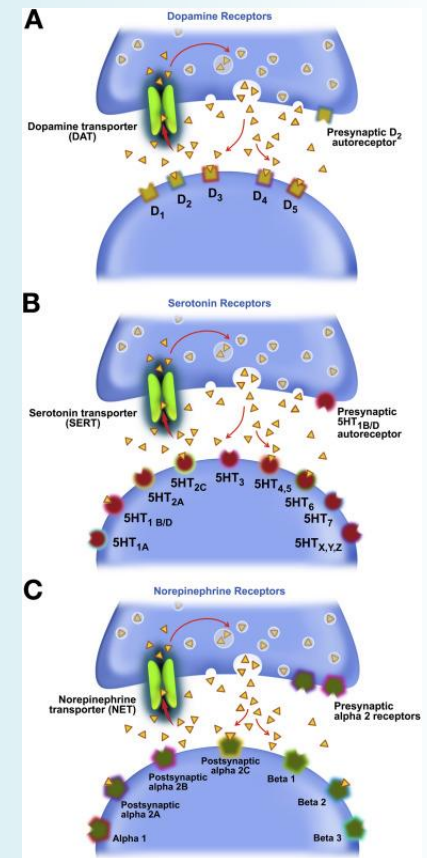


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# Prescribing antidepressants in IBS smartly

- Overall efficacy<sup>1</sup>.
  - TCAs more effective than SSRIs for pain
  - SSRIs should be a second-line agent or a first-line agent in pts w/ comorbid anxiety, depression, social anxiety
  - SNRIs extensively studied for fibromyalgia and diabetic neuropathy but can be useful in IBS-C or in those who failed TCA trial
- Leverage side effects to correct patient's motility
  - TCAs in IBS-D (use anticholinergic side effects)
  - Emerging data for pregabalin (?IBS-M)<sup>2</sup>.



SNRI, serotonin norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

Sobin WH, Heinrich TW, *et al. Am J Gastroenterol.* 2017 May;112(5):693-702

Saito YA, Almazar AE, *et al. Aliment Pharmacol Ther.* 2019 Feb;49(4):389-397.

Image: Drossman DA, Tack J, *et al. Gastroenterology.* 2018 Mar;154(4):1140-1170. e1.



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# Matching treatment to predominant symptoms

= FDA-approved

Predominant symptom?

## Abdominal pain

- Anti-spasmodics
- Peppermint oil
- Low FODMAP
- Antidepressants
- Linaclotide
- Plecanatide
- Eluxadoline
- Tegaserod
- Tenapanor

## Constipation

- Soluble fiber
- OTC laxatives
- Lubiprostone
- Linaclotide
- Plecanatide
- Tenapanor
- Tegaserod

## Bloating

- Low-FODMAP
- Antidepressants
- Linaclotide
- Plecanatide
- Rifaximin
- Eluxadoline
- Tegaserod

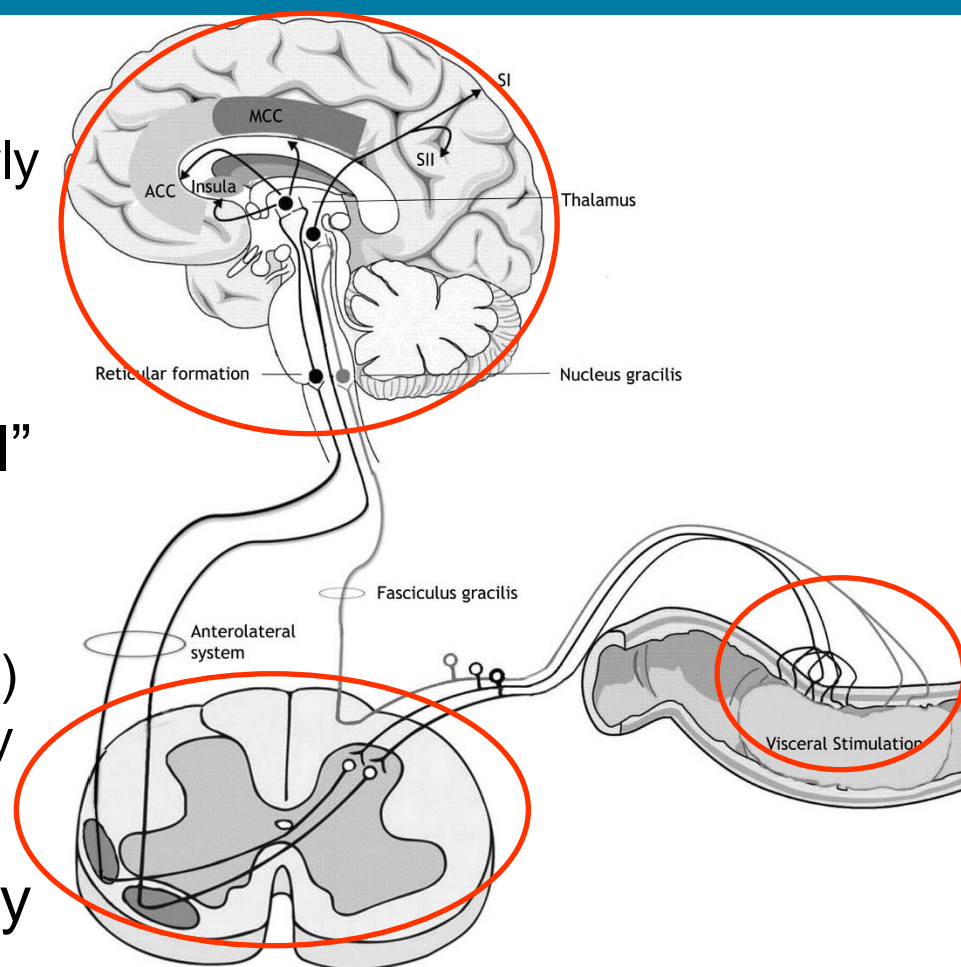
## Diarrhea

- Loperamide
- Soluble fiber
- Low-FODMAP
- Rifaximin
- Alosetron
- Eluxadoline
- Ondansetron



# How I explain IBS

- Visceral hypersensitivity
  - Normal gut sensations improperly amplified in PNS and CNS
  - Abnormal sensory response to normal physiologic processes
- Treatment is a “3-legged stool”
  - Motility agents (laxatives, anti-diarrheals)
  - Neuromodulators (TCAs, SSRIs) and cognitive behavioral therapy
  - Dietary changes/probiotics
- Investing time up front can pay dividends later on



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# Summary

- Key Points

1. Most GERD patients need long-term treatment
2. The absolute risks of long-term PPI use are low, but not zero
3. Best people to send for upper endoscopy: alarm symptoms, new GERD over age 55, heavy white men who smoke, unusual symptoms
4. Most IBS does not need a colonoscopy
5. The low-FODMAP diet is a powerful, patient-centered tool but has limitations
6. Evidence for probiotics is still very limited
7. Match IBS treatment to patient's predominant symptom
8. IBS is fundamentally a disorder of brain-gut interaction; neuromodulators can and should be used early



# Thank you



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