All Roads Lead to Rome, But You Can't Get There From Here: Confident Diagnosis and Management of Chronic Abdominal Pain

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May 1, 2021

Maine AAP Annual Spring Conference

Disclosures

- None

Objectives – Illustrated with a Case

1. All Roads Lead to Rome but You Can't Get There from Here: Looking for Red Flags in the Evaluation of Chronic Abdominal Pain and Using Rome Criteria to Diagnose Functional GI Disorders
2. Using what is known about the physiology of functional gastrointestinal disorders to convey diagnostic confidence and set the stage for recommending therapies
3. Implementing pharmacologic, non-pharmacologic, and dietary therapies for functional gastrointestinal disorders

Rome Criteria

- Symptom-based guidelines by which child and adolescent functional gastrointestinal disorders (FGID) can be diagnosed
- Combination of evidence and expert clinician consensus
- 2016: Rome IV

Gastroenterology 2016; 150: 1456-1468

Rome Criteria

Childhood Functional Gastrointestinal Disorders: Child/ Adolescent

Jeffrey S. Hyams,[1,*] **Carlo Di Lorenzo,**[2,*] Miguel Saps,[2] Robert J. Shulman,[3] Annamaria Staiano,[4] and Miranda van Tilburg[5]

Table 1. Functional Gastrointestinal Disorders: Children and Adolescents

H1. Functional nausea and vomiting disorders
- H1a. Cyclic vomiting syndrome
- H1b. Functional nausea and functional vomiting
- H1c. Rumination syndrome
- H1d. Aerophagia

H2. Functional abdominal pain disorders
- H2a. Functional dyspepsia
- H2b. Irritable bowel syndrome
- H2c. Abdominal migraine
- H2d. Functional abdominal pain—not otherwise specified

H3. Functional defecation disorders
- H3a. Functional constipation
- H3b. Nonretentive fecal incontinence

Gastroenterology 2016; 150: 1456-1468

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Part 1
Case – 15 year old female

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Case – 15 year old female

- Chief complaint: Generalized (sometimes upper) Abdominal Pain.
- Present for at least the last 6 months. Happens almost every day.
- In the upper abdomen. Feels "kinda like bloating, kinda like burning." Some nausea, no vomiting.
- Though it can be present any time, it is most often made worse by oral intake. She tends to feel very full. There is no relation to bowel movements, which are soft and regular. No blood in the stool.
- No weight loss.
- Missing at least 2 days of school every week.
- Normal CBC, CMP, ESR, CRP, TTG-IgA. Negative Stool H pylori. Normal stool calprotectin.
- No response to proton pump inhibitor.

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Differential Diagnosis

- Functional Gastrointestinal Disorder
- GERD
- EoE
- Celiac
- IBD
- Gastroparesis
- SIBO
- Eating Disorder
- Endometriosis
- Biliary Disease

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What's NOT going on here

Table 2. Potential Alarm Features in Children With Chronic Abdominal Pain[a]

Family history of inflammatory bowel disease, celiac disease, or peptic ulcer disease
Persistent right upper or right lower quadrant pain
Dysphagia
Odynophagia
Persistent vomiting
Gastrointestinal blood loss
Nocturnal diarrhea
Arthritis
Perirectal disease
Involuntary weight loss
Deceleration of linear growth
Delayed puberty
Unexplained fever

Gastroenterology 2016; 150: 1456-1468

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Can you make a diagnosis?

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Rome IV - Functional Dyspepsia

H2a. Diagnostic Criteria[a] for Functional Dyspepsia

Must include 1 or more of the following bothersome symptoms at least 4 days per month:

1. Postprandial fullness
2. Early satiation
3. Epigastric pain or burning not associated with defecation
4. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

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Rome IV - Irritable Bowel Syndrome

H2b. Diagnostic Criteria[a] for Irritable Bowel Syndrome

Must include all of the following:

1. Abdominal pain at least 4 days per month associated with one or more of the following:
   a. Related to defecation
   b. A change in frequency of stool
   c. A change in form (appearance) of stool
2. In children with constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not irritable bowel syndrome)
3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

[a]Criteria fulfilled for at least 2 months before diagnosis.

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Rome IV – FAP-NOS

H2d. Diagnostic Criteria[a] for Functional Abdominal Pain–NOS

Must be fulfilled at least 4 times per month and include all of the following:

1. Episodic or continuous abdominal pain that does not occur solely during physiologic events (eg, eating, menses)
2. Insufficient criteria for irritable bowel syndrome, functional dyspepsia, or abdominal migraine
3. After appropriate evaluation, the abdominal pain cannot be fully explained by another medical condition

[a]Criteria fulfilled for at least 2 months before diagnosis.

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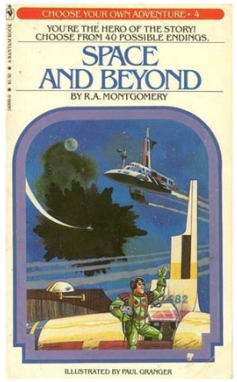
Now can you make a diagnosis?

- No Red Flags
- History could certainly be consistent with Functional Dyspepsia
- Appropriate Evaluation?



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Appropriate Evaluation?

- The most appropriate evaluation is the one that allows:
  - Provider to be satisfied with the diagnosis
  - Patient and family to be satisfied with the diagnosis
- *Satisfied = Able to tolerate the remaining uncertainty and move forward with non-specific therapies to target symptoms of functional disorders rather than continuing to perseverate on/wonder "what's wrong?"

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Can you make a diagnosis YET?

- Rome III: "no evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explain the subject's symptoms"
- Rome IV: "after appropriate medical evaluation, the symptoms cannot be attributed to another medical condition"
- Paradigm shift from a diagnosis of exclusion to diagnosis in a positive fashion based on clinical criteria.

Gastroenterology 2016; 150: 1456-1468

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PERSPECTIVE TOLERATING UNCERTAINTY

BECOMING A PHYSICIAN

Tolerating Uncertainty — The Next Medical Revolution?

Arabella L. Simpkin, B.M., B.Ch., M.M.Sc, and Richard M. Schwartzstein, M.D.

"…it seems clear that technology will perform the routine tasks of medicine for which algorithms can be developed. Our value as physicians will lie in the gray-scale space, where we will have to support patients who are living with uncertainty — work that is essential to strong and meaningful doctor–patient relationships."

NEJM 2016; 1: 1456-1468

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Final Diagnosis?

Functional Dyspepsia

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Summary 1

- Identification of Red Flags is helpful in the evaluation of chronic abdominal pain.
- Functional Gastrointestinal Disorders can be diagnosed in a positive fashion based on clinical criteria.
- An appropriate evaluation is one that allows the provider and the patient to tolerate the uncertainty inherent in a functional diagnosis and move forward with therapy

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Functional Dyspepsia – Dude, What??

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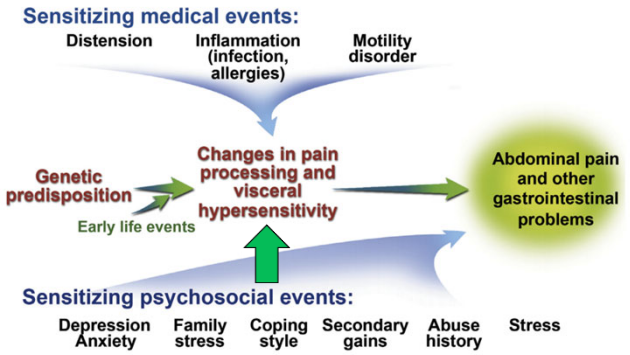
Concepts in Pathophysiology



Gastroenterology 2016; 150: 1456-1468

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Pathophysiology??

- **Disordered gut-brain axis**
  - Abnormalities in 5-hydroxytryptamine (5-HT) metabolism.
- Dietary effects
- Genetic factors
- Infections and disturbances in the intestinal microbiota
- Low-grade mucosal inflammation
- Immune activation
- Altered intestinal permeability
- Disordered bile salt metabolism

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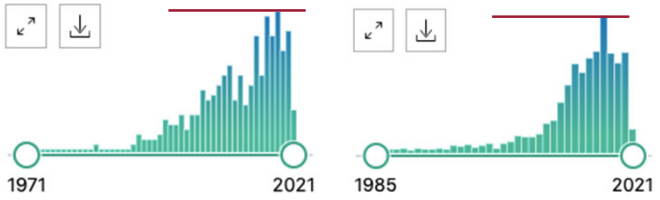
Limited Knowledge Based

Crohn's: 318.5/100,000 = 0.3%

Pain-Predominant FGID: 15%

Functional -28 hits Ped Crohn's 128 hits



J Pediatr 2018; 195:134-139 *Lancet* 2017; 390:2769-2778 Pubmed

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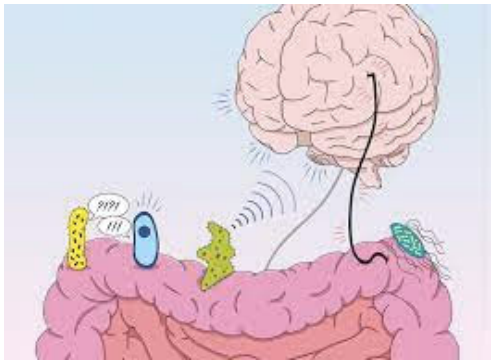
But there's still A LOT we know



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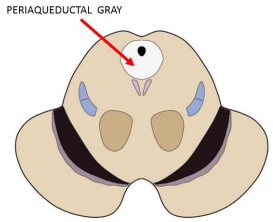
PAG: Relevance to Chronic Pain

- Area of the brain known to have an important role in pain processing
- Since 2001, differences in periaqueductal gray matter activity and/or connectivity have been associated with:
  - irritable bowel syndrome
  - primary dysmenorrhea
  - migraine
  - chronic low back pain



Gastroenterology 2001;120:369-376
Neurogastroenterol Motil 2017;29:c13060

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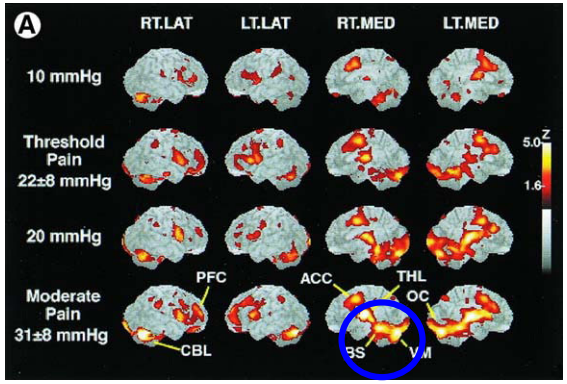
Disordered Brain-Gut Axis: Starts with PAG



Brainstem Periaqueductal Gray Matter

Gastroenterology 2001;120:369-376

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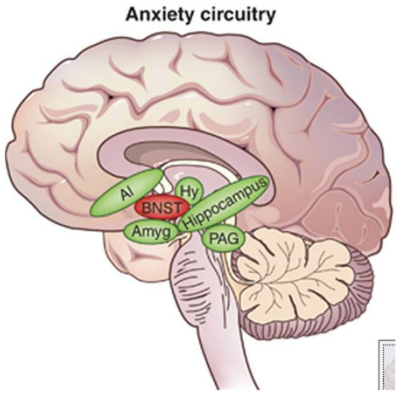
PAG: Relevance to Chronic Anxiety

- PAG has significant functional connections to the bed nucleus of the stria terminalis (BNST)
- BNST seems to have an important role in stress response and in anxiety and addiction
- Anxiety and FGIDs are commonly co-morbid



Neuropsychopharmacology REVIEWS 2016;41:126-141

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Anxiety: Chicken or Egg?

- 12 year prospective survey study.
  - 1775 initially surveyed, 1002 completed follow-up (60%)
- Higher baseline anxiety predicted development of FGID 12 years later
- Baseline FGID predicted higher levels of anxiety and depression 12 years later
- Brain-Gut connection may be bidirectional

Gut 2012;61:1284-1290

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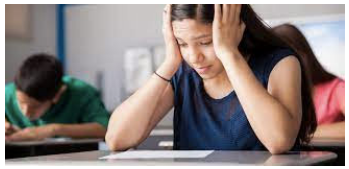
Summary 2



- Periaqueductal Gray is important in pain processing and signaling.
- Visceral pain shares some CNS signaling pathways with chronic anxiety (through the PAG).
- There may be a bidirectional relationship between anxiety, depression, and chronic GI pain.

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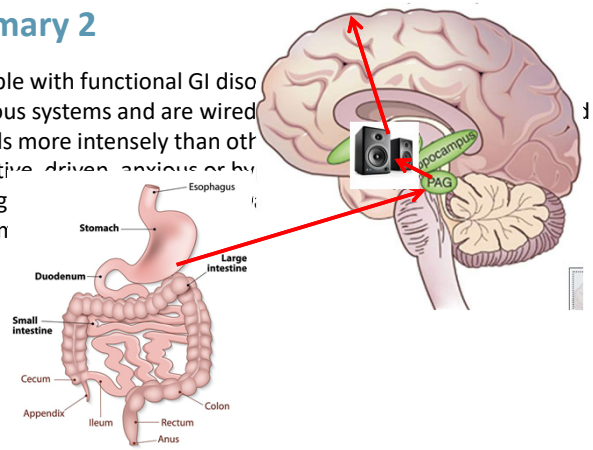
Summary 2

- "People with functional GI diso
  nervous systems and are wired
  signals more intensely than oth
  sensitive, driven, anxious or by
  wiring
  abdon



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Pharmacologic Therapy

- Cyproheptadine
- Amitriptyline
- Citalopram
- Peppermint Oil
- *Cochrane Database Syst Rev* 2017 Review conclusion: "…There is currently no convincing evidence to support the use of drugs to treat RAP in children. Well-conducted clinical trials are needed to evaluate any possible benefits and risks of pharmacologic interventions..."

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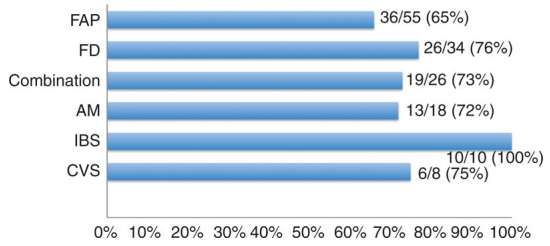
Cyproheptadine Use in Children With Functional Gastrointestinal Disorders

*†Shailender Madani, †Orlando Cortes, and ‡Ronald Thomas

Retrospective, Single Center, Single Clinician



Conclusion: cyproheptadine effective for improving symptoms of FGIDs

JPGN 2016;62:409-413

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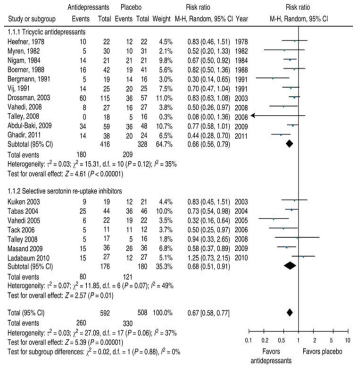
Antidepressants

TCA and SSRI are effective in adults



Am J Gastroenterol 2014;109:1350–1365
Neurogastroenterol Motil 2014;26:1642–1650

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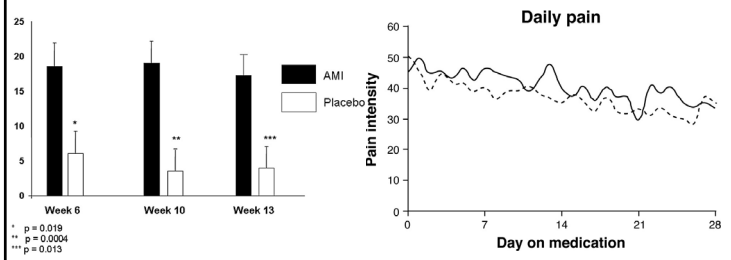
Amitriptyline

- RCT: AMI vs Placebo
- Primary Outcome: QoL
- AMI > Placebo

J Pediatr 2008;152:685-9

- RCT: AMI vs Placebo
- Primary Outcome: Pain
- Significant improvement in sx over time
- No difference between AMI and placebo

Gastroenterology 2009;137:1261–1269



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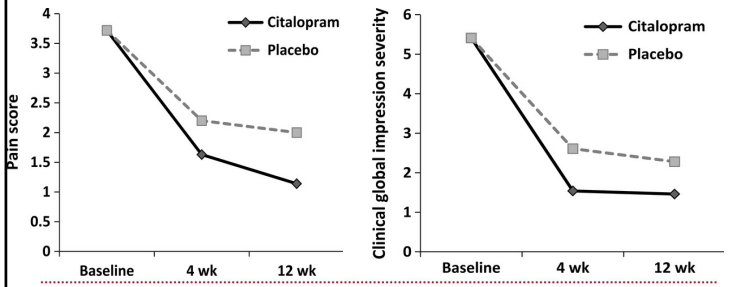
Citalopram

RCT: CIT vs Placebo

Primary Outcome: Pain

Difference not significant, both groups improved

Neurogastroenterol Motil 2014;26:1642–1650



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Peppermint Oil

RCT: Peppermint Oil vs Placebo

Primary Outcome: Pain

Significant Difference with improvement in peppermint oil group

J Pediatr 2001;138:125-128

Treatment		Much worse	Worse	No effect	Better	Much better
Peppermint oil	Frequency	0	0	6	6	9
	Percent	0	0	29	29	42
Placebo	Frequency	2	4	6	9	0
	Percent	10	19	28	43	0

*$P < .002$.

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Non-Pharmacologic Therapy

- Meditation/Mindfulness
- Hypnotherapy
- Cognitive Behavioral Therapy
- *Cochrane Database Syst Rev* 2017 Review conclusion: "…data from trials to date provide some evidence for beneficial effects of CBT and hypnotherapy in reducing pain in the short term in children and adolescents presenting with RAP… there were insufficient data to explore effects of treatment by RAP subtype."

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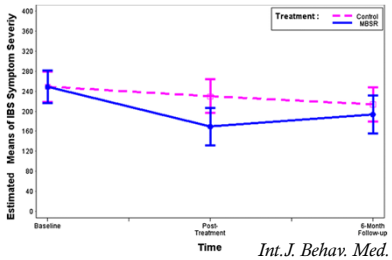
Meditation

Mindfulness-Based Stress Reduction for the Treatment of Irritable Bowel Syndrome Symptoms: A Randomized Wait-list Controlled Trial

RCT: mindfulness program vs waitlist
Primary Outcome: IBS symptom scale
Clinically meaningful decrease in symptom severity



Int.J. Behav. Med. 2013;20:385–396

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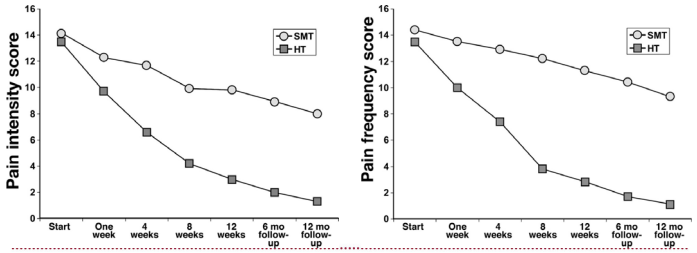
Hypnotherapy

Hypnotherapy for Children With Functional Abdominal Pain or Irritable Bowel Syndrome: A Randomized Controlled Trial

RCT: Gut-directed hypnotherapy vs standard care
Outcomes: Pain intensity score, frequency score
Significant improvement in pain freq and intensity
Gastroenterology 2007;133:1430–1436



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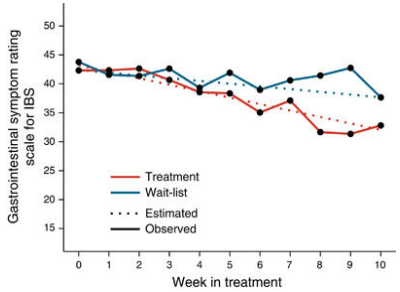
Cognitive Behavioral Therapy

Internet-Delivered Cognitive Behavior Therapy for Adolescents With Irritable Bowel Syndrome: A Randomized Controlled Trial

RCT: iCBT vs waitlist control
Outcome: IBS symptom scale
Statistical Improvement in symptom scale over time in the treatment group
Am J Gastroenterol 2017;112:152-162



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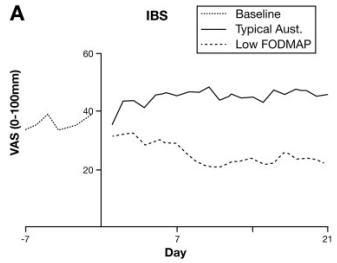
Dietary Interventions

- Low-FODMAP Diet
- Probiotics
- *Cochrane Database Syst Rev* 2017 Review conclusion: "…moderate to low quality evidence suggesting that probiotics may be effective in improving pain in children with RAP...there was no convincing evidence that fibre-based interventions improve pain in children with RAP...future trials of low FODMAP diets...are also required..."

Low FODMAP Diet

- FODMAP = Fermentable oligosaccharides, disaccharides, monosaccharides and polyols
- As a result of poor absorption, these carbohydrates may contribute to gastrointestinal symptoms.
  - Luminal Distension (osmotic)
  - Rapid Fermentation
- Low FODMAP diet comprehensively limits consumption of fermentable carbohydrates.
- Evidence for efficacy in Adults



Gastroenterology 2014;146:67–75

Randomised clinical trial: gut microbiome biomarkers are associated with clinical response to a low FODMAP diet in children with the irritable bowel syndrome

- Randomized cross-over design with 7 day washout period.
- FODMAP group: 1.1/day
- TACD group: 1.4/ day P < 0.05
- **Modest, significant improvement**

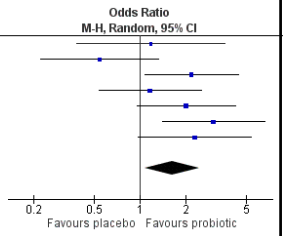
Aliment Pharmacol Ther 2015; 42: 418–427

Probiotics

Multiple RCTs.
Multiple different strains/products used.
Favorable pooled analysis

Study or Subgroup	Probiotic Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bausserman 2005	11	25	10	25	9.7%	1.18 [0.38, 3.63]
Eftekhari 2015	15	40	21	40	13.1%	0.54 [0.22, 1.32]
Francavilla 2010	48	67	37	69	16.7%	2.18 [1.07, 4.45]
Gawronska 2007	25	52	23	52	15.4%	1.17 [0.54, 2.53]
Giannetti 2017	25	73	15	73	16.0%	2.01 [0.96, 4.24]
Guandalini 2010	44	59	29	59	15.3%	3.03 [1.40, 6.60]
Saneian 2015	27	45	17	43	13.8%	2.29 [0.98, 5.39]
Total (95% CI)		**361**		**361**	**100.0%**	**1.63 [1.07, 2.47]**
Total events	195		152			

Heterogeneity: Tau² = 0.14; Chi² = 10.89, df = 6 (P = 0.09); I² = 45%
Test for overall effect: Z = 2.27 (P = 0.02)



Cochrane Database Syst Rev. 2017 Mar 23;3:CD010972

Weaknesses of the Literature

- Few controlled trials
  - Small sample sizes
  - Not reproduced
- Heterogeneous populations
  - All use Rome criteria
  - Some include all pain-predominant syndromes
- Heterogeneous outcomes
  - Most are reported by the subject
- No comparisons of interventions

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Summary 3

- There are many safe pharmacologic, non-pharmacologic, and dietary interventions that can be considered to treat functional gastrointestinal disorders.
- All have been studied in small scale and generally have relatively small effect compared to placebo.
- Few to none have been studied on a large scale or reproduced.
- And if you were paying attention to some of those graphs…

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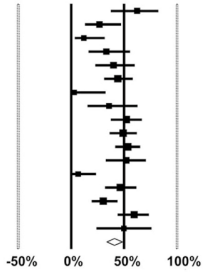
Placebo

Study name	Improvement rate (%)	Lower limit	Upper limit
Christensen[67] 1982	62.5	37.7	82.1
Feldman et al[66] 1985	26.9	13.4	46.7
See et al[51] 2001	12.0	3.9	31.3
Kline et al[55] 2001	33.3	16.8	55.3
Bausserman et al[58] 2005	40.0	23.0	59.7
Gawrońska et al[59] 2007	44.2	31.5	57.8
Bahar et al[57] 2008	2.8	0.2	32.2
Sadeghian et al[62] 2008	35.7	15.7	62.4
Saps et al[56] 2009	52.3	37.7	66.4
Guandalini et al[53] 2010	49.2	36.7	61.7
Francavilla et al[60] 2010	53.6	41.9	65.0
Di Nardo et al[52] 2013	52.0	33.1	70.4
Romano et al[54] 2013	6.7	1.7	23.1
Horvath et al[61] 2013	46.5	32.3	61.3
Pourmoghaddas et al[42] 2014	30.4	19.8	43.5
Karunanayake et al[49] 2015	59.5	44.3	73.1
Zybach et al[65] 2016	50.0	24.4	75.6
Pooled	40.9	33.6	48.6



41% of patients improve with placebo!

J Pediatr 2017;182:155-163

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Placebo

"Placebo studies also reveal the value of social interaction as a treatment for pain...researchers studied patients in pain from irritable bowel syndrome and found that 44 percent of those given sham acupuncture had adequate relief from their symptoms.

If the person who performed the acupuncture was extra supportive and empathetic, however, that figure jumped to 62 percent."

- NY Times, 1/9/2016

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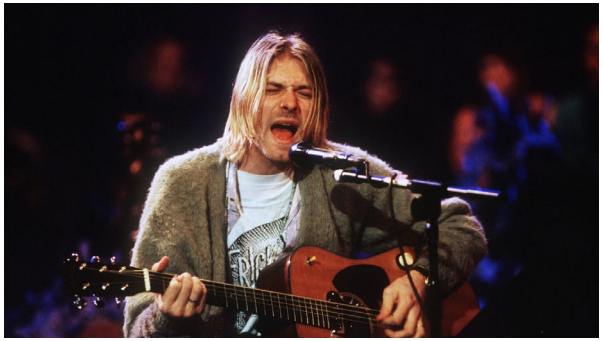
Grand Summary

- Though our understanding of their physiology is incomplete, Functional Gastrointestinal Disorders should be diagnosed in a positive fashion.
  - Objective evaluation should target tolerance of the uncertainty inherent in a functional diagnosis.
- There is evidence to suggest that there are difference in neurological signaling (brain-gut interaction) between people with and without FGIDs.
- There are many safe pharmacologic, non-pharmacologic, and dietary therapies that can be considered for treatment of FGIDs.
  - Ultimately our time, validation, and empathy may be just as important as any of them

IBS Pop Culture Quiz

"Thank you all from the burning pit of my nauseous stomach"



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