A Smooth Sea Never Made a Skilled Sailor: Navigating the Brain-Gut Axis

Noah Hoffman, MD, MSHP

Maine AAP Spring Conference
March 29, 2025

1

Disclosures

None of the planners or speakers for this event have any financial relationships to disclose.

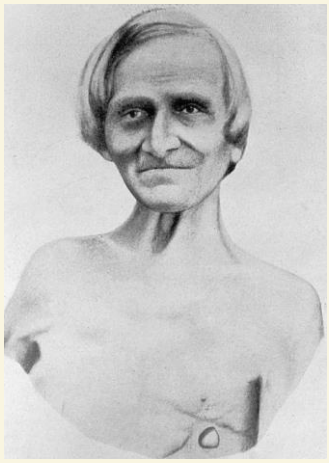
2

Objectives

- Learn to use what is known about the physiology of disorders of gut-brain interaction to convey diagnostic confidence and set the stage for therapeutic recommendations.
- Prepare to implement pharmacologic and non-pharmacologic therapies for DGBI in the medical home.
- Why?

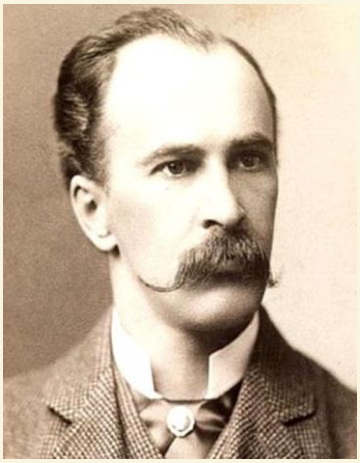
40 20 55 .300

Historical Context



- Alexis St. Martin, Canadian Fur Trader, **Voyageur**
- Shot at close range in 1822, left with G-C fistula
- Treated by Dr. William Beaumont, then became his "servant."
- Complained of abdominal pain often.
- Beaumont inserted food into St. Martin's stomach, then later removed it to observe the extent of digestion
- When St. Martin was angry or irritable, changes in the rate of digestion were noted.

Inspiration



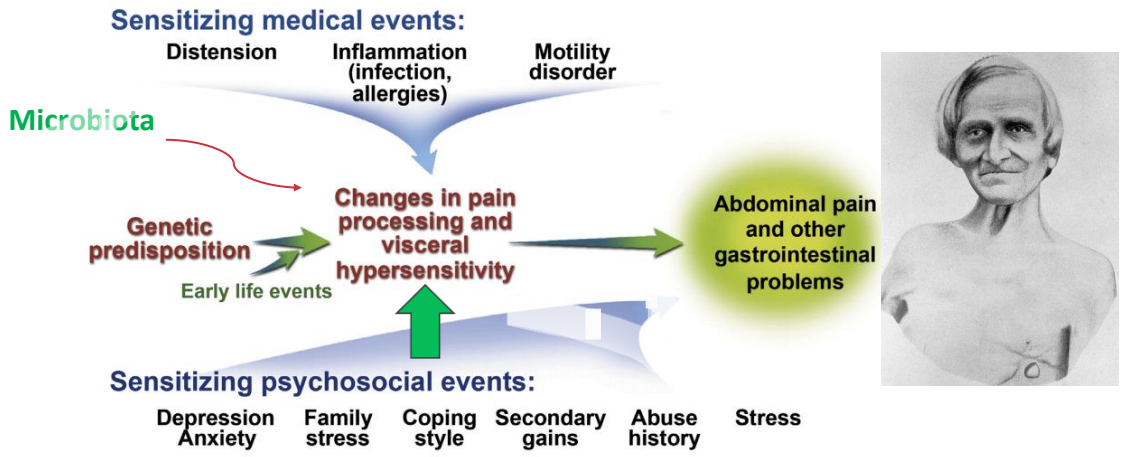
"It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has."

MaineHealth Barbara Bush Children's

PATIENT CENTERED RESPECT INTEGRITY EXCELLENCE OWNERSHIP INNOVATION 5

5

Pathophysiology Summary



Gastroenterology 2016; 150: 1456-1468

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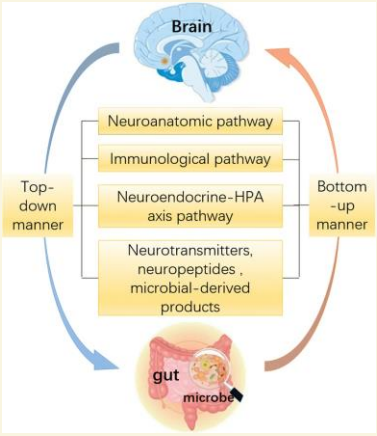
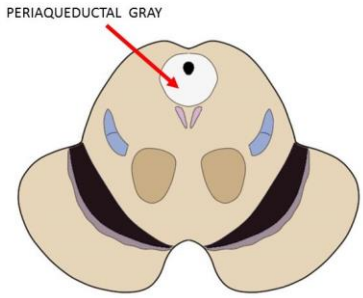
Pathophysiology



- Some specifics of Brain-Gut neurophysiology
- New understanding: Microbiome
- Clinical Context
- Summary and Primary Care Action Steps

Pathophysiology: PAG mediates Chronic Pain

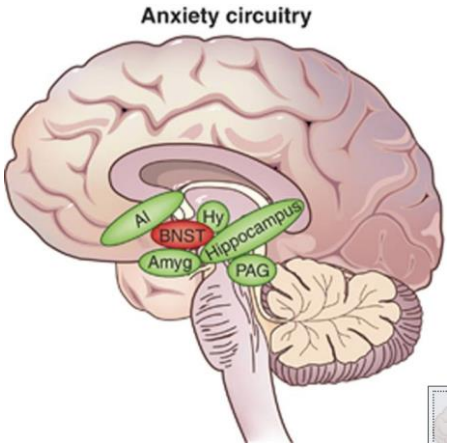
- Area of the brain known to have an important role in pain processing
- Differences in periaqueductal gray matter activity and/or connectivity have been associated with:
  - irritable bowel syndrome
  - primary dysmenorrhea
  - migraine
  - chronic low back pain



Gastroenterology 2001;120:369-376
Neurogastroenterol Motil 2017;29:e13060

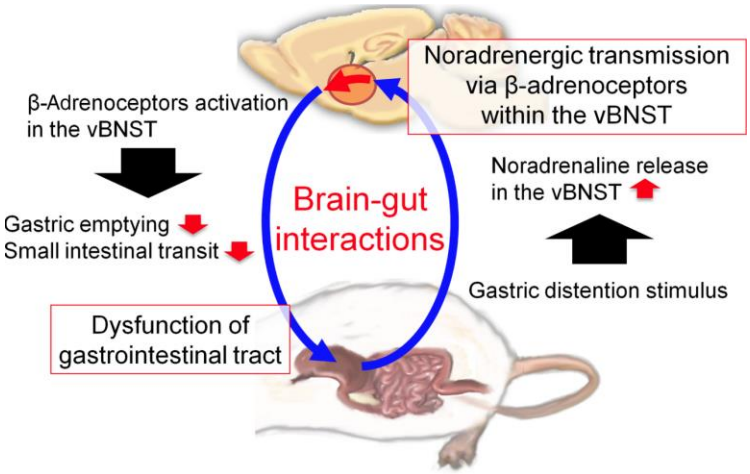
Pathophysiology: PAG/BNST relationship

- 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



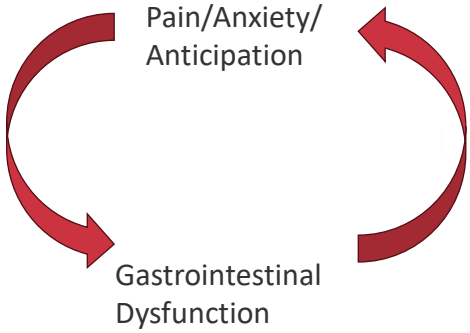
Neuropsychopharmacology REVIEWS 2016;41:126-141

Pathophysiology: BNST/Gut Relationship



Neuropsychopharmacol Rep 2018;38(1):37-43

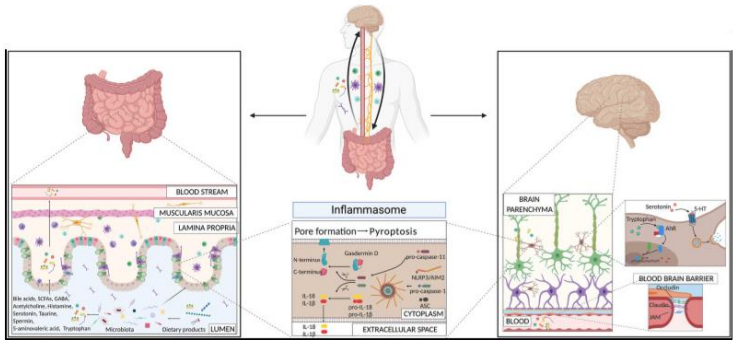
PAG/BNST/Gut Vicious Cycle



New Directions: Microbiota-Gut-Brain Axis

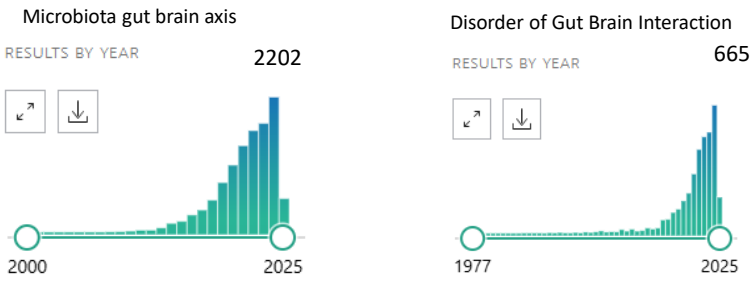
Two-way communication between the brain and gut microbiota:

- microbial byproducts
- immune and inflammatory pathway
- neuroendocrine and enteroendocrine signaling
- stress response and the vagus nerve



Front Immunol 2020 Dec 10:11:604179

New Directions: Microbiota-Gut-Brain Axis



Clinical Context: Anxiety

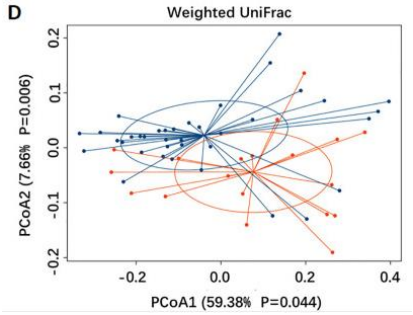
- 12 year prospective survey study.
  - 1775 initially surveyed, 1002 completed follow-up (60%)
- Higher baseline anxiety predicted development of FGID 12 years later
- Baseline FGID predicted higher levels of anxiety and depression 12 years later
- Clinical evidence of Brain-Gut connection bidirectionality

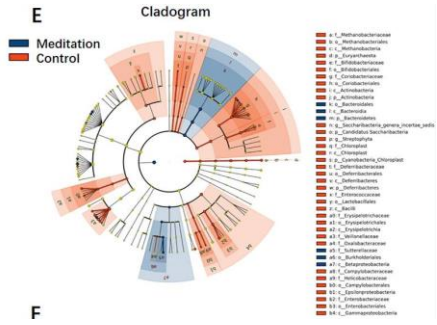
Gut 2012;61:1284-1290

Clinical Context: Microbiome

Alteration of faecal microbiota balance related to long-term deep meditation

Stool samples from 37 Buddhist monks (mediation) vs matched local residents (no meditation)

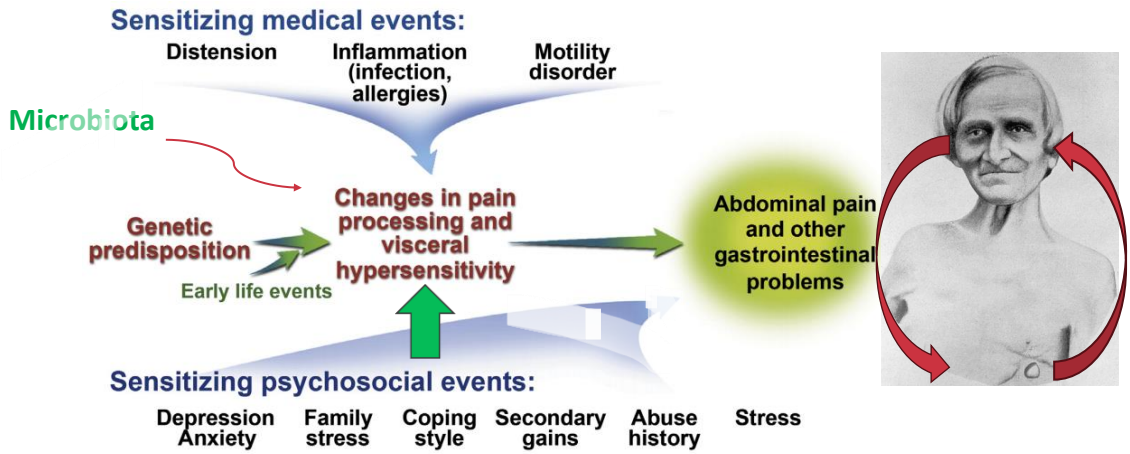




Clinical Evidence of connection between CNS and microbiome

Gen Psychiatr. 2023 Jan 3;36(1):e100893

Pathophysiology Summary



Gastroenterology 2016; 150: 1456-1468

Pathophysiology Summary

- "Because of nervous system physiology, life experiences, and microbiome variables, people with disorders of gut-brain interaction are wired to feel gastrointestinal signals more intensely than other people. They are often sensitive, driven, anxious or hypervigilent people because the wiring that makes them that way is the same wiring that drives abdominal pain."
- "We need to break the cycle of reactivity and turn down the sensitivity of the nervous system in order to help you feel better."

Inspiration

"I don't know if I'm elated or gassy but I'm somewhere in that zone."

How can we make the diagnosis of Disorder of Gut-Brain Interaction?

Diagnosis Of DGBI

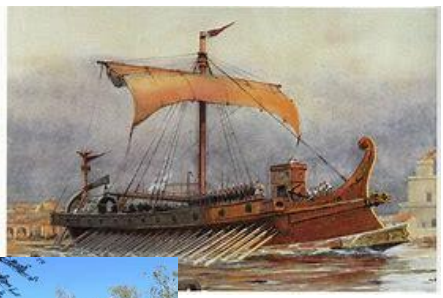
Step 1 – Know the patient and take a history, evaluate for alarm symptoms

Step(s) 2 – **E**xclude/**E**valuate, **E**mpathize**,** **E**ducate

Step 3 – Positive Diagnosis Based on Rome Criteria

Rome Criteria

- Symptom-based criteria by which child and adolescent functional gastrointestinal disorders (FGID) can be diagnosed
- Combination of evidence and expert clinician consensus
- 2016: Rome IV
  - Rome V expected 2026, change to DGBI terminology



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

Take a History

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

Evaluate/Exclude

- 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?"
- Considerations include CBC, inflammatory markers, CMP, celiac
  - From there, considers testing to address specific symptoms/risks

Empathize, Educate

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

Then Diagnose in a Positive Fashion

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 burr
4. After appropriate evalu another medical condi

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 defeca
   b. A change in frequ
   c. A change in form
2. In children with constipat the constipation (childre constipation, not irritable
3. After appropriate evaluat another medical conditio

[a]Criteria fulfilled for at least 2 m

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

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

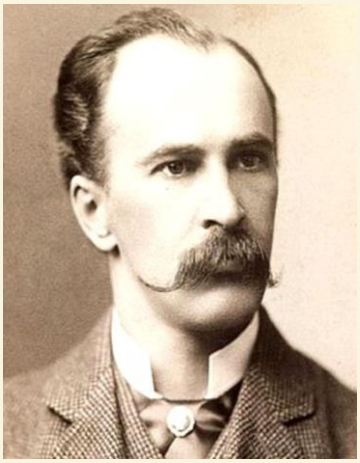
1. Episodic or continuous abdominal pain that does not occur solely during physiologic events (eg, eating, menses)
2. Insufficient criteria for irritable bowel syndrome, functional dyspepsia, or abdominal migraine
3. After appropriate evaluation, the abdominal pain cannot be fully explained by another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

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

PCP Action Steps!

- Understand patients and their symptoms thoroughly.
- Discuss the differential diagnosis of symptoms and explain why you do or do not think they should be considered.
  - Introduce concept of DGBI to any patient with chronic GI symptoms.
  - Discuss turning down the sensitivity of the nervous system.
  - Educate patients and families confidently.
- Order targeted tests you are comfortable with before referring.

Inspiration



"He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all."

Non-Pharmacologic Therapy (Lifestyle measures)

- Function in School
- Regulate Sleep Cycle
- Avoid substances
- Exercise Regularly

Non-Pharmacologic Therapy (Brain-Gut Behavioral Therapies)

- 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."

Meditation

Mindfulness-based stress reduction improves irritable bowel syndrome (IBS) symptoms via specific aspects of mindfulness

Prospective Cohort: mindfulness program vs waitlist
Primary Outcome: IBS symptom scales
Clinically meaningful decrease in symptom severity

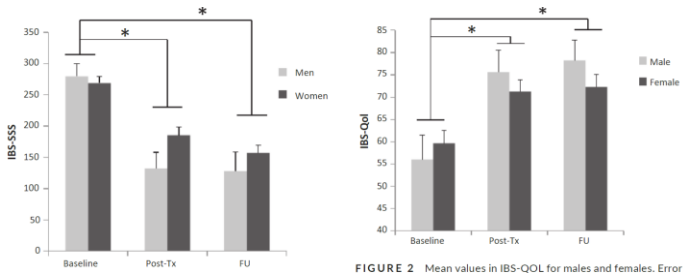


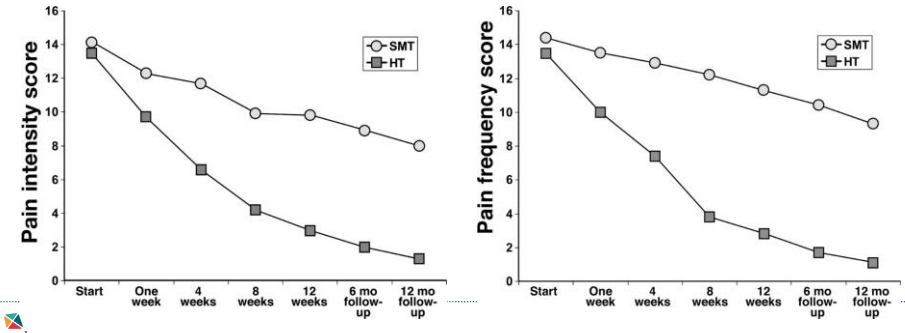
FIGURE 2 Mean values in IBS-QOL for males and females. Error

Neurogastro & Motility. 2020;32:e13828

Hypnotherapy

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

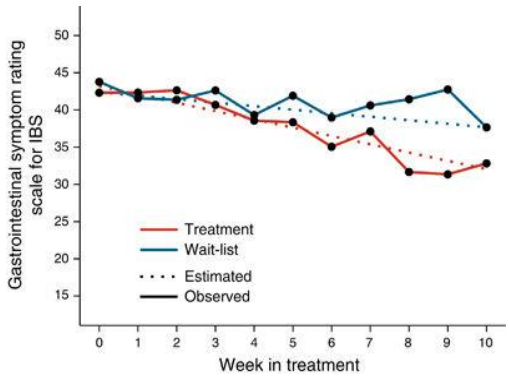
RCT: Gut-directed hypnotherapy vs standard care
Outcomes: Pain intensity score, frequency score
Significant improvement in pain freq and intensity
Gastroenterology 2007;133:1430–1436



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

Non-Pharmacologic Therapy Summary

"BGBTs are clinician administered, short-term, non pharmacologic interventions that prioritize the remediation of GI symptoms over improvement of psychological co-morbidity, although the latter is also possible."

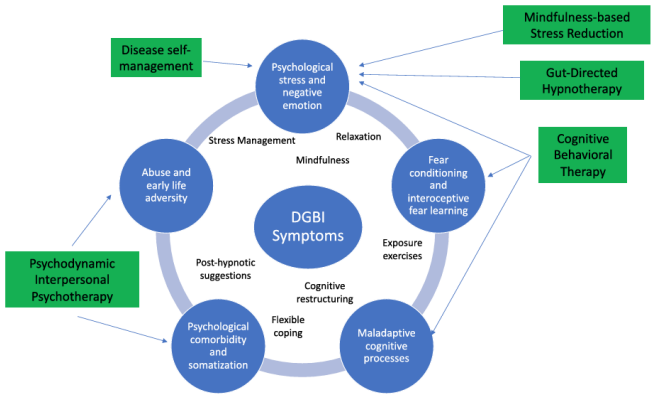


Figure 1. Brain-Gut behavior therapy targets and techniques by class.

Gastroenterology 2022;162:300-315

Pharmacologic Therapy

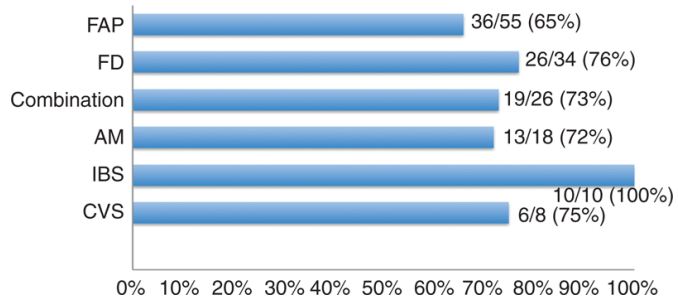
- Cyproheptadine
- Amitriptyline
- Citalopram/SSRIs
- Peppermint Oil
- *Cochrane Database Syst Rev* 2017 Review conclusion: "…There is currently no convincing evidence to support the use of drugs to treat RAP in children. Well-conducted clinical trials are needed to evaluate any possible benefits and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

Cyproheptadine

Cyproheptadine Use in Children With Functional Gastrointestinal Disorders

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

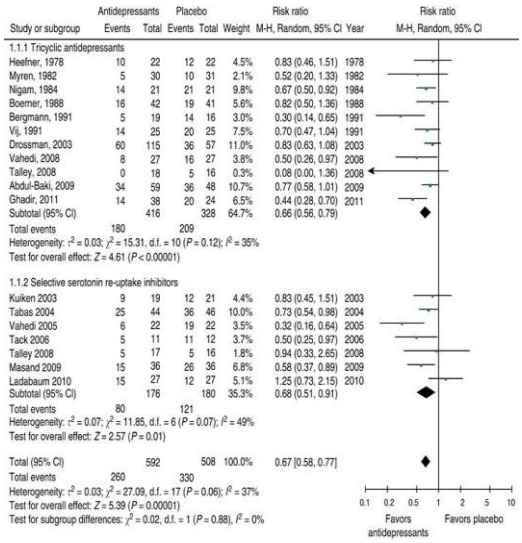
Retrospective, Single Center, Single Clinician



Conclusion: cyproheptadine effective for improving symptoms of FGIDs

JPGN 2016;62:409-413

Antidepressants



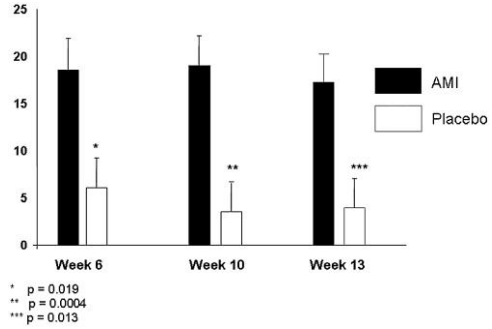
TCA and SSRI are effective vs placebo in adults

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

Amitriptyline

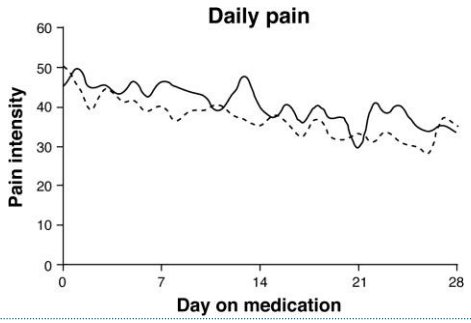
- RCT: AMI vs Placebo
- Primary Outcome: QoL
- AMI > Placebo

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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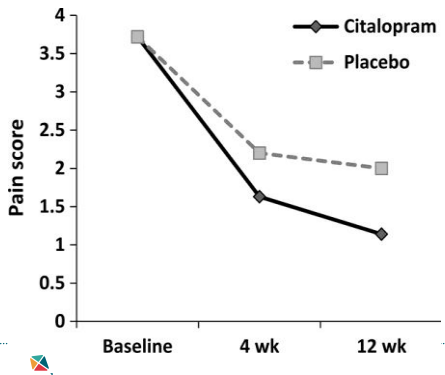
Citalopram

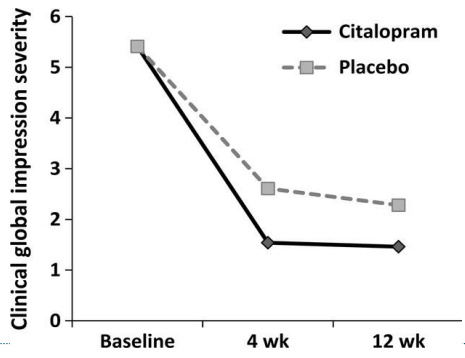
RCT: CIT vs Placebo

Primary Outcome: Pain

Difference not significant, both groups improved

Neurogastroenterol Motil 2014;26:1642–1650





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Gabapentin

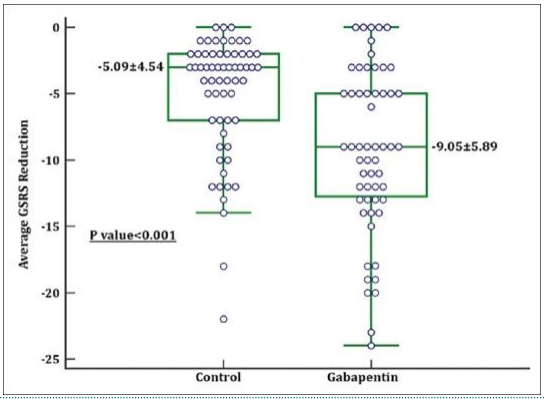
Randomized Controlled Trial

omeprazole vs omeprazole plus gabapentin

Primary Outcome: Symptom Rating Scale

Symptom scale lower in the gabapentin group

Adv Biomed Res 2019;8:53



Peppermint Oil

RCT: Peppermint Oil vs Placebo

Primary Outcome: Pain

Significant Difference with improvement in peppermint oil group

J Pediatr 2001;138:125-128

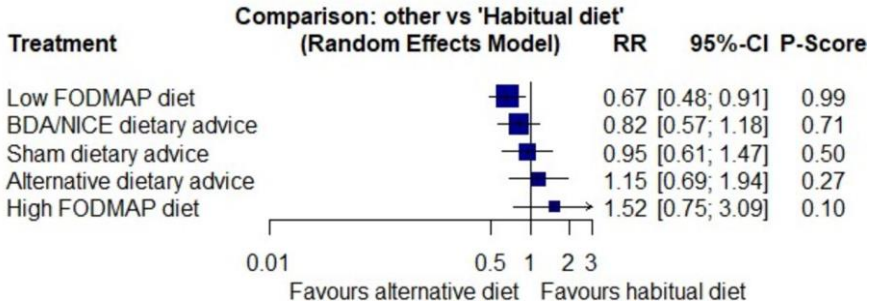
Treatment		Much worse	Worse	No effect	Better	Much better
Peppermint oil	Frequency	0	0	6	6	9
	Percent	0	0	29	29	42
Placebo	Frequency	2	4	6	9	0
	Percent	10	19	28	43	0

*$P < .002$.

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



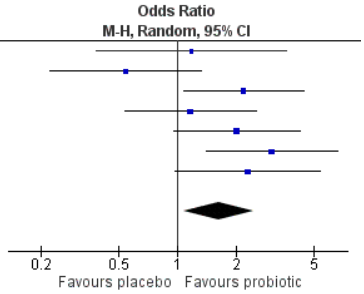
Gut 2022; 71(6): 1117–1126

Probiotics

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

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
  - Largely subjective
- Few comparisons of interventions

Pharmacotherapy Summary

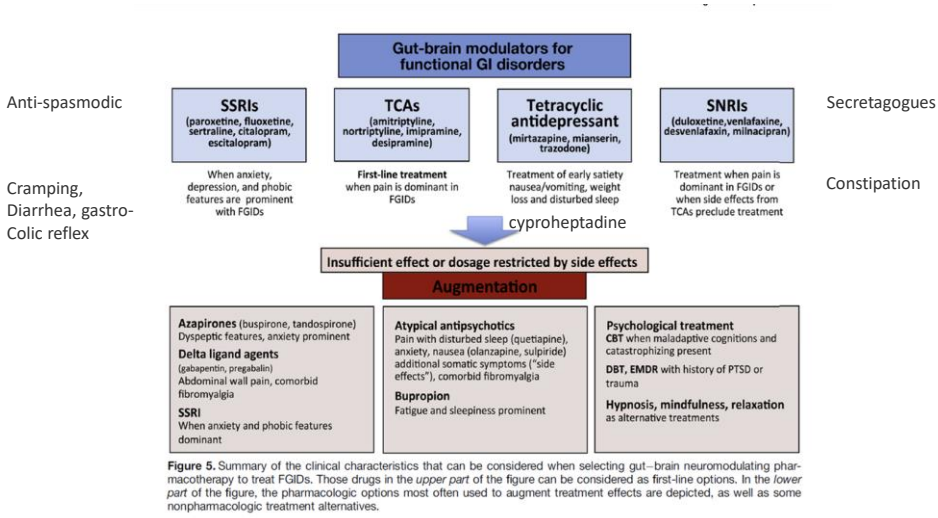


Figure 5. Summary of the clinical characteristics that can be considered when selecting gut--brain neuromodulating pharmacotherapy to treat FGIDs. Those drugs in the *upper part* of the figure can be considered as first-line options. In the *lower part* of the figure, the pharmacologic options most often used to augment treatment effects are depicted, as well as some nonpharmacologic treatment alternatives.

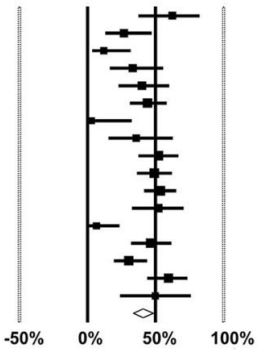
DGBI Therapy Summary

- There are multiple safe non-pharmacologic, pharmacologic, and dietary interventions that can be considered to treat disorders of gut-brain interaction.
- All have been studied in small scale and when applicable 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…

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

Placebo rate and 95% CI



41% of patients improve with placebo!

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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

PCP Action Steps!

- Follow-up with patients after they are referred or after you start (or after we recommend) a therapy, monitor response to therapy.
- Help students and families navigate school avoidance and encourage them to attend school.
- Become familiar with and utilize resources:
  - Non-pharmacologic therapists in your offices/communities
  - Neuromodulating medications
- Take over stable prescriptions and follow-up.

Summary

- Though our understanding of their physiology is incomplete, Disorders of Gut-Brain Interaction should be diagnosed in a positive fashion.
  - Objective evaluation should target tolerance of the uncertainty inherent in a DGBI diagnosis.
- There is evidence to suggest that there are differences in neurological signaling (brain-gut interaction) between people with and without FGIDs.
- There are many safe non-pharmacologic, 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.
- "A Smooth Sea Never Made a Skilled Sailor."

Thank you!