Irritable Bowel Syndrome

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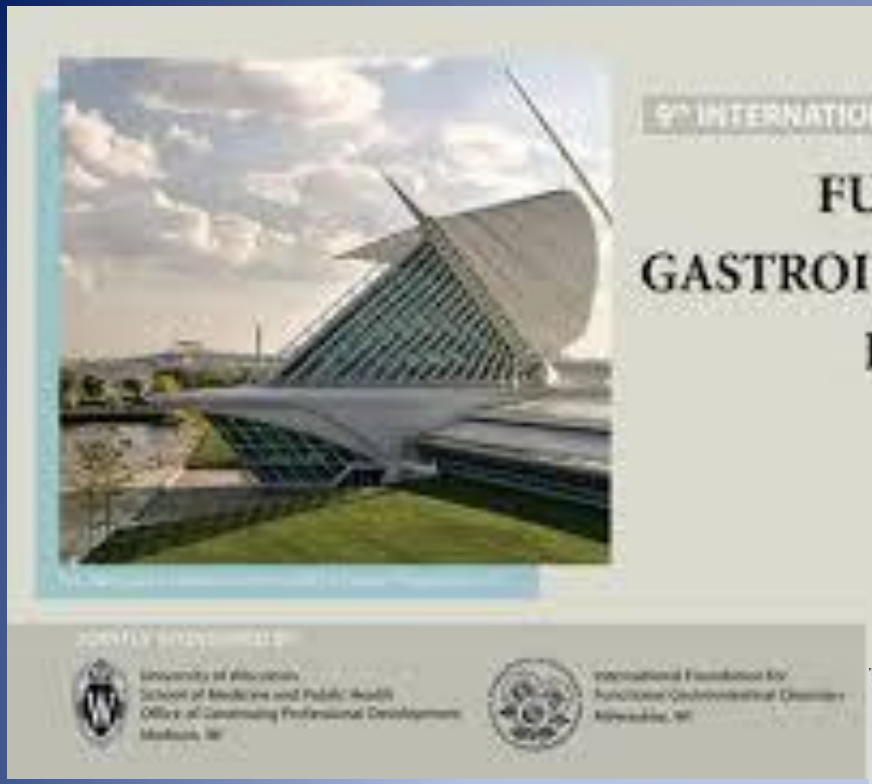
דוקטור

- כואבת לי הבטן המון זמן
- אני משלשלת , אבל גם סובלת מעצירות
- יש לי נפיחות והמון גזים
- הייתי כבר אצל המון גסטרואנטרולוגים, ואף אחד לא עזר לי

- ד"ר, מה יש לי? (ד"ר תציל אותי....)

IBS: Patient's concerns



Definition of FGID

- Chronic and recurrent symptoms of the gastrointestinal (GI) tract:
  - **Pain, nausea, vomiting, bloating, diarrhea, constipation**
- Without detectable structural or biochemical abnormalities


ROME III
The
Functional
Gastrointestinal
Disorders

Table 1 : Rome III diagnostic criteria for functional dyspepsia.

At least 3 months, with onset at least 6 months previously, of one or

(including upper endoscopy)

doms

Table 1. Symptom-Based Criteria (Rome III) for the Diagnosis of IBS

Recurrent abdominal pain or discomfort at least 3 days per month for the past 3 months, with symptom onset >6 months before diagnosis, associated with two or more of the following:

- Improvement with defecation
- Change in frequency of stool
- Change in stool form (appeara

IBS: irritable bowel syndrome. Sou

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- Change in stool form (appearance)

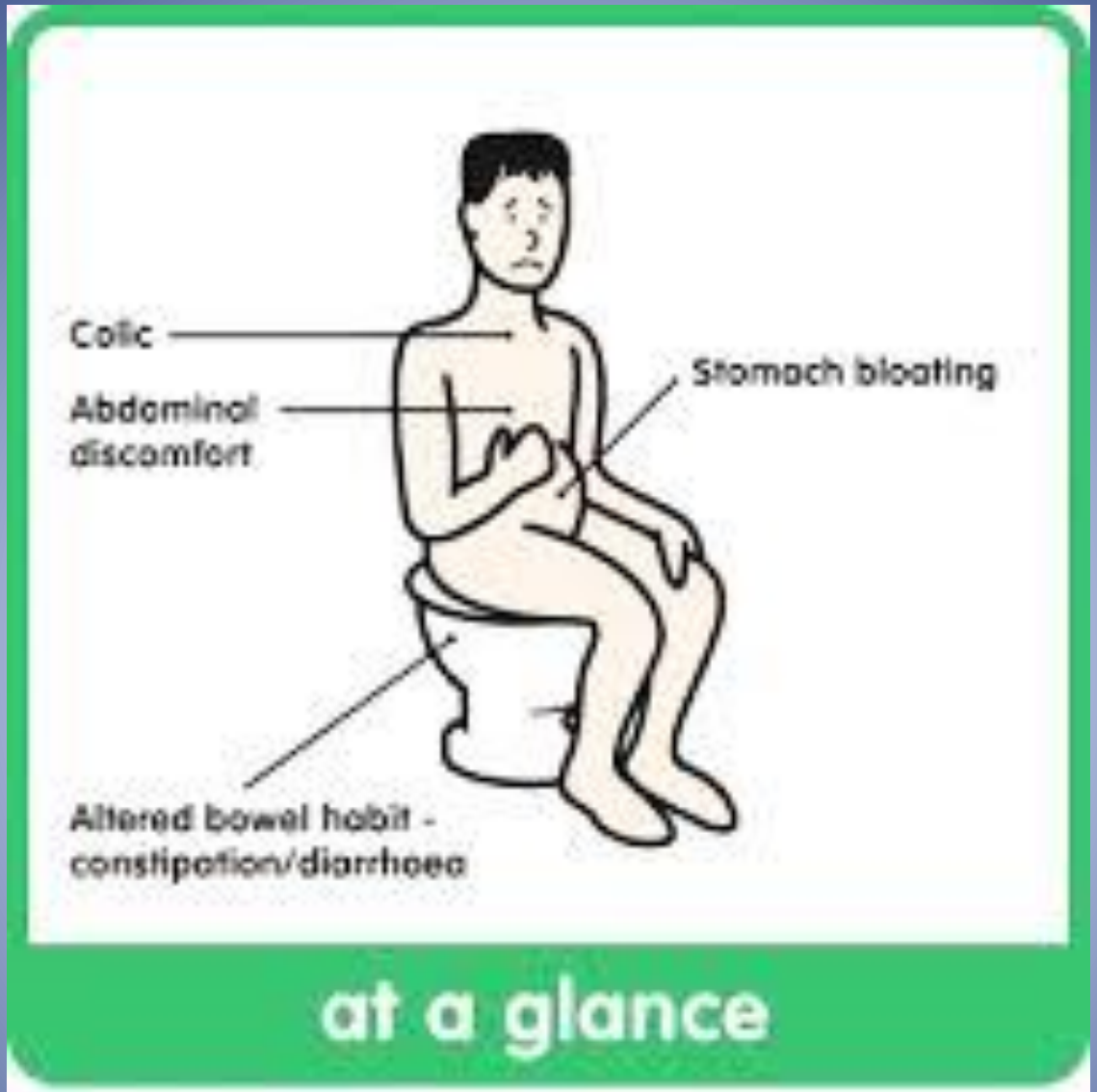
IBS: irritable bowel syndrome. Source: Reference 7.

Epigastric pain syndrome
Symptoms of at least three months' duration, with onset at least six months before, ALL of the following criteria
Pain and/or burning that is
1. Intermittent
2. Located in the epigastrium
3. Of at least moderate to severe intensity
4. At least once a week
and:
1. Is not generalized to, or located in, other abdominal or thoracic regions
2. Is not associated with defecation or flatulence
3. Does not fulfill criteria for disorders of the gallbladder or sphincter of Oddi

Table 2. Rome III: Diagnostic Criteria for Functional Constipation[a]

1. Must include ≥2 of the following:
   - Straining at defecation[b]
   - Lumpy/hard stools[b]
   - Sensation of incomplete evacuation[b]
   - Sensation of anorectal obstruction/blockage[b]
   - Manual maneuvers to facilitate defecation[b]
   - Fewer than 3 defecations/wk
2. Loose stools rarely present without use of laxatives
3. Insufficient criteria for IBS

[a]Criteria must be fulfilled for last 3 mo with six onset ≥6 mo prior to diagnosis.



Irritable Bowel Syndrome (IBS)

Table 1. Symptom-Based Criteria (Rome III) for the Diagnosis of IBS

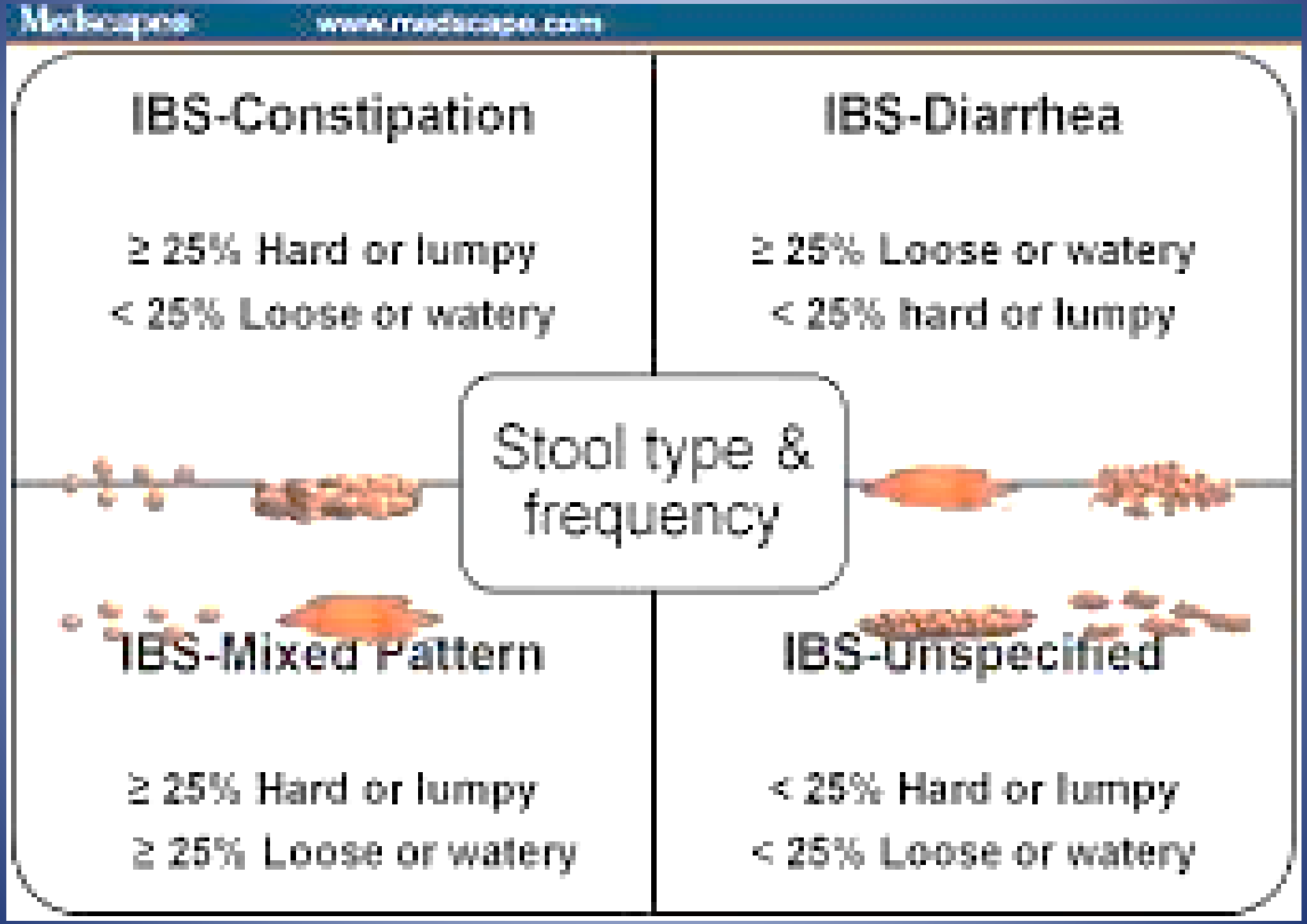
No pathological finding

- Change in frequency of stool
- Change in stool form (appearance)

IBS: irrita

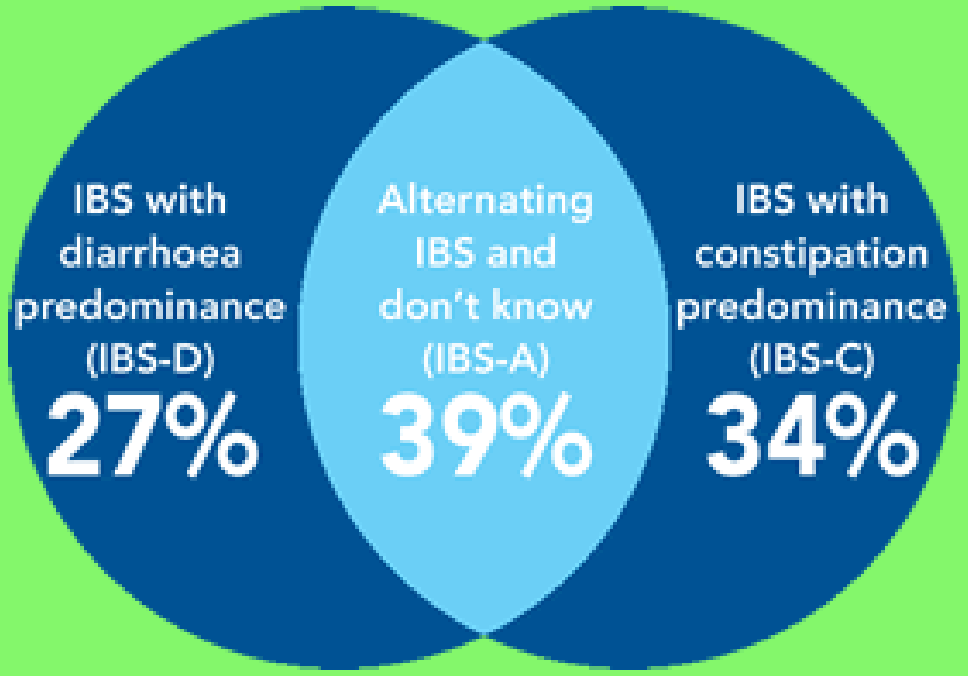
No pain, No IBS

IBS Subtypes



CLASSIFYING IBS

The three categories



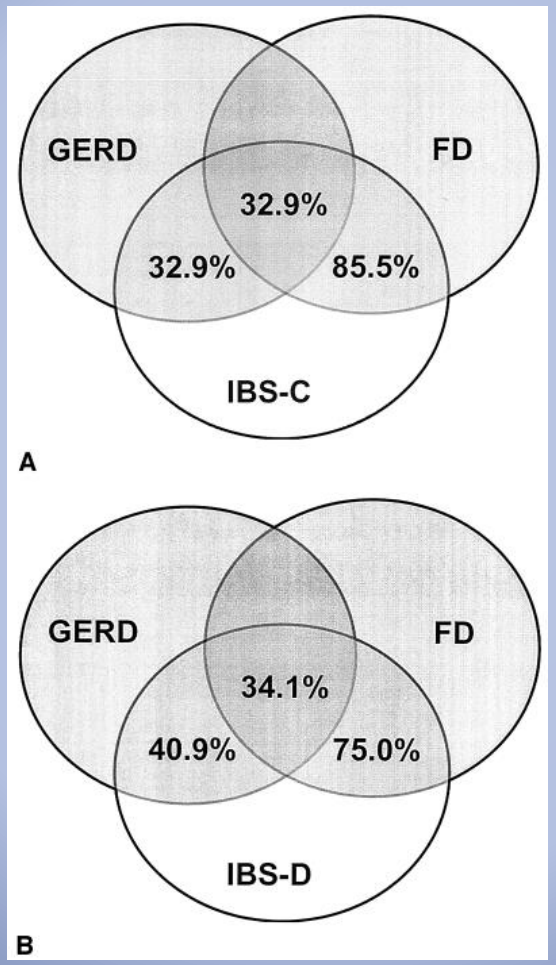
* The classification of an IBS case may influence its subsequent management

Overlap with Other Functional Gastrointestinal Disorders

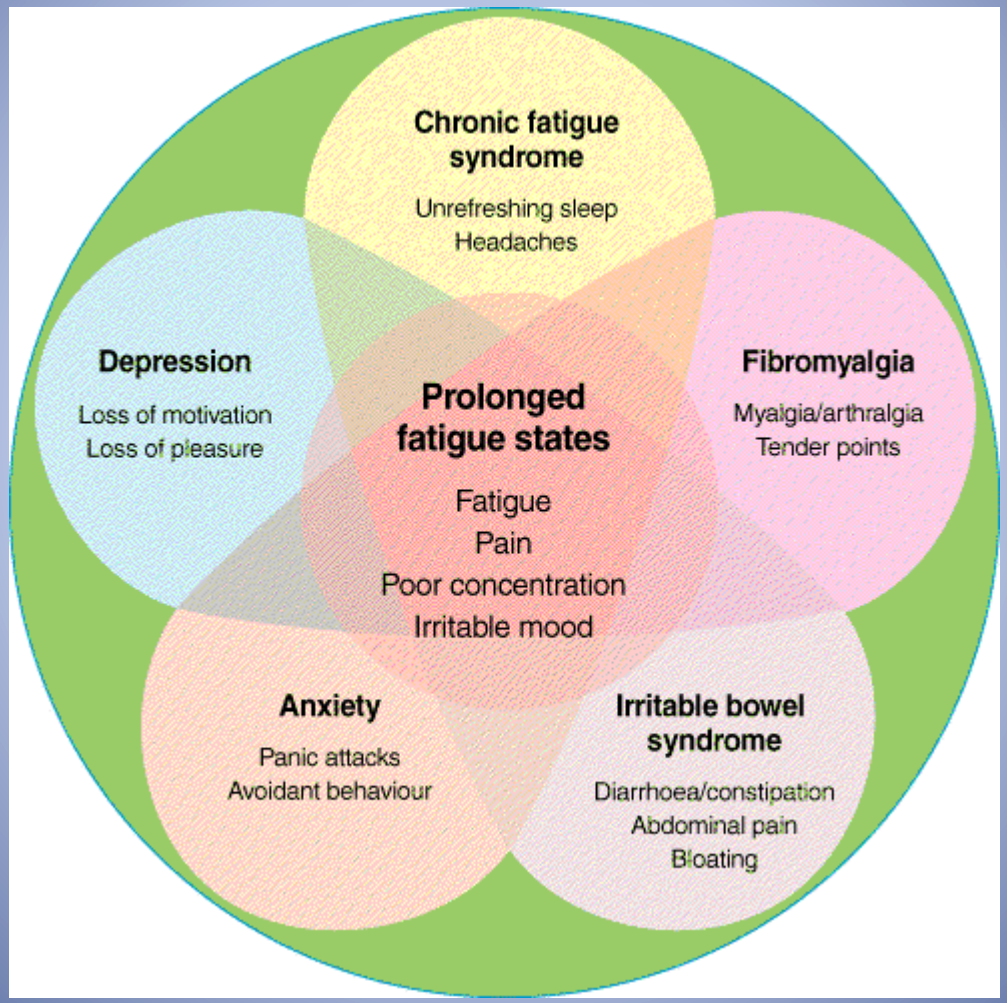
- Many population-based and clinical studies have reported the associations with other diseases, specifically other FGIDs.

- GERD and symptomatic bronchial hyper-responsiveness occurred more frequently together with IBS than expected.

Overlap with Other Functional Gastrointestinal Disorders



Overlap with Extra intestinal Disorders



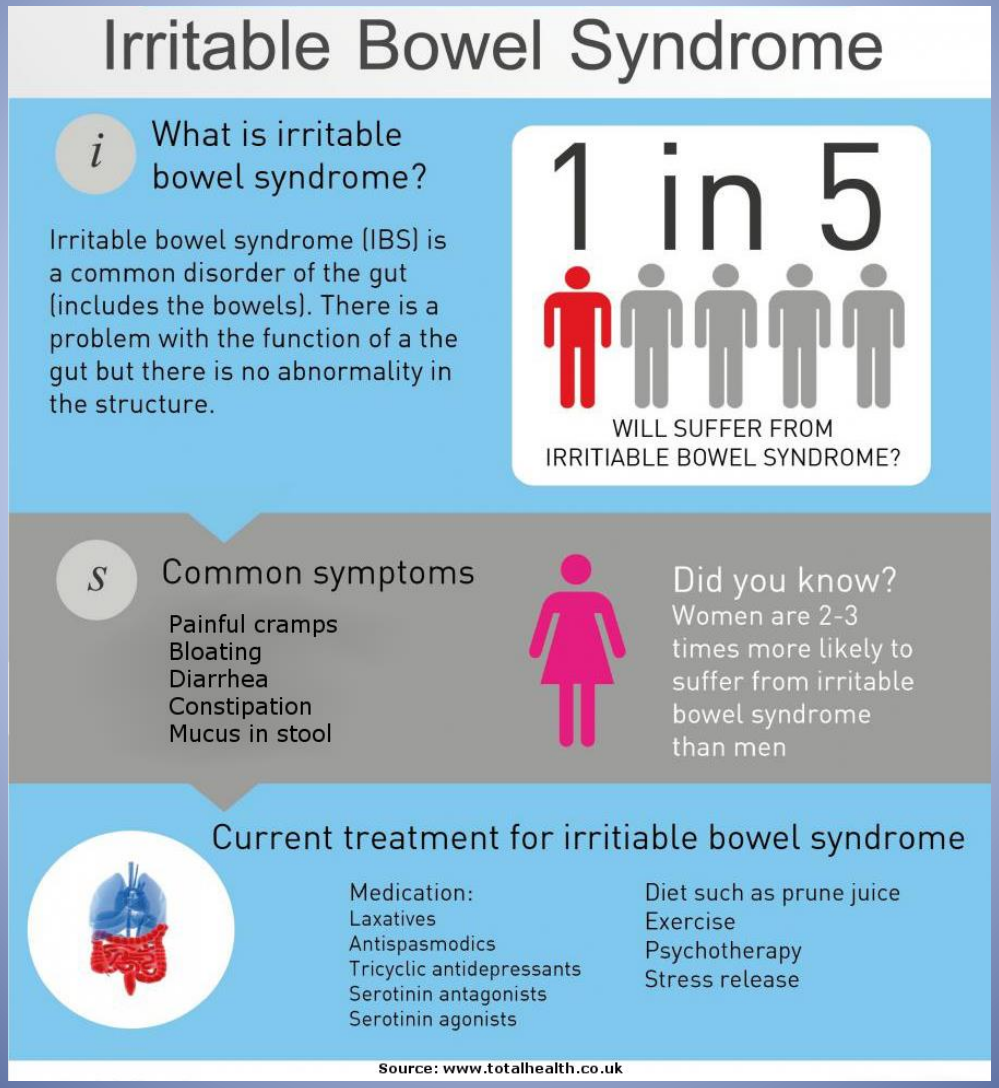
Natural history of IBS

- IBS is considered a chronic stable disorder that may wax and wane for years.
- Substantial symptom fluctuation among the GI symptom complexes with increasing prevalence over time.
- IBS is not associated with any increase in mortality.

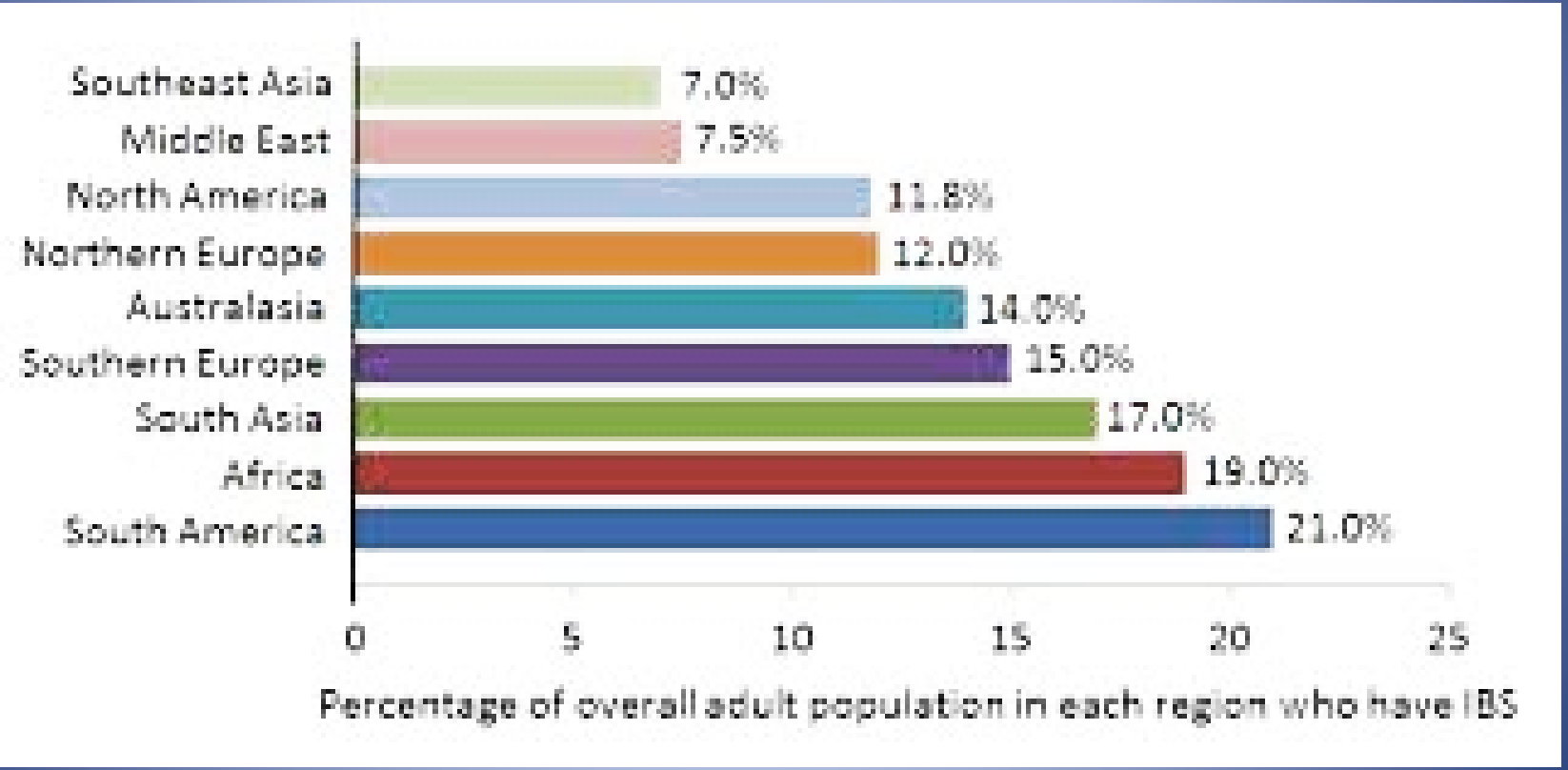
Table 5 | Development of IBS, retained, lost and developed in 10 years

	n	Never IBS (%)	Lost IBS (%)	Retained IBS (%)	Developed IBS (%)
Manning	674	56.2	12.2	19.1	12.5
Self-report	621	74.9	8.5	8.2	8.4
Rome III	749	81.4	5.7	4.3	8.7

Epidemiology



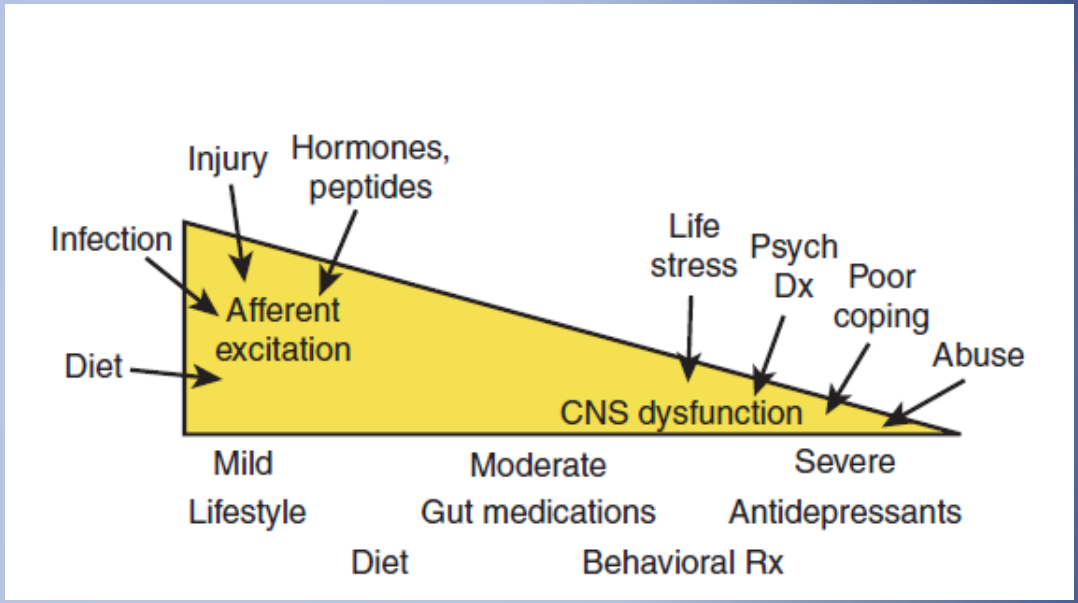
Worldwide Distribution of IBS




IBS is about 1.5x more common in women than in men*
3 in 10 with IBS have diarrhea*
1 in 4 cases is considered severe*

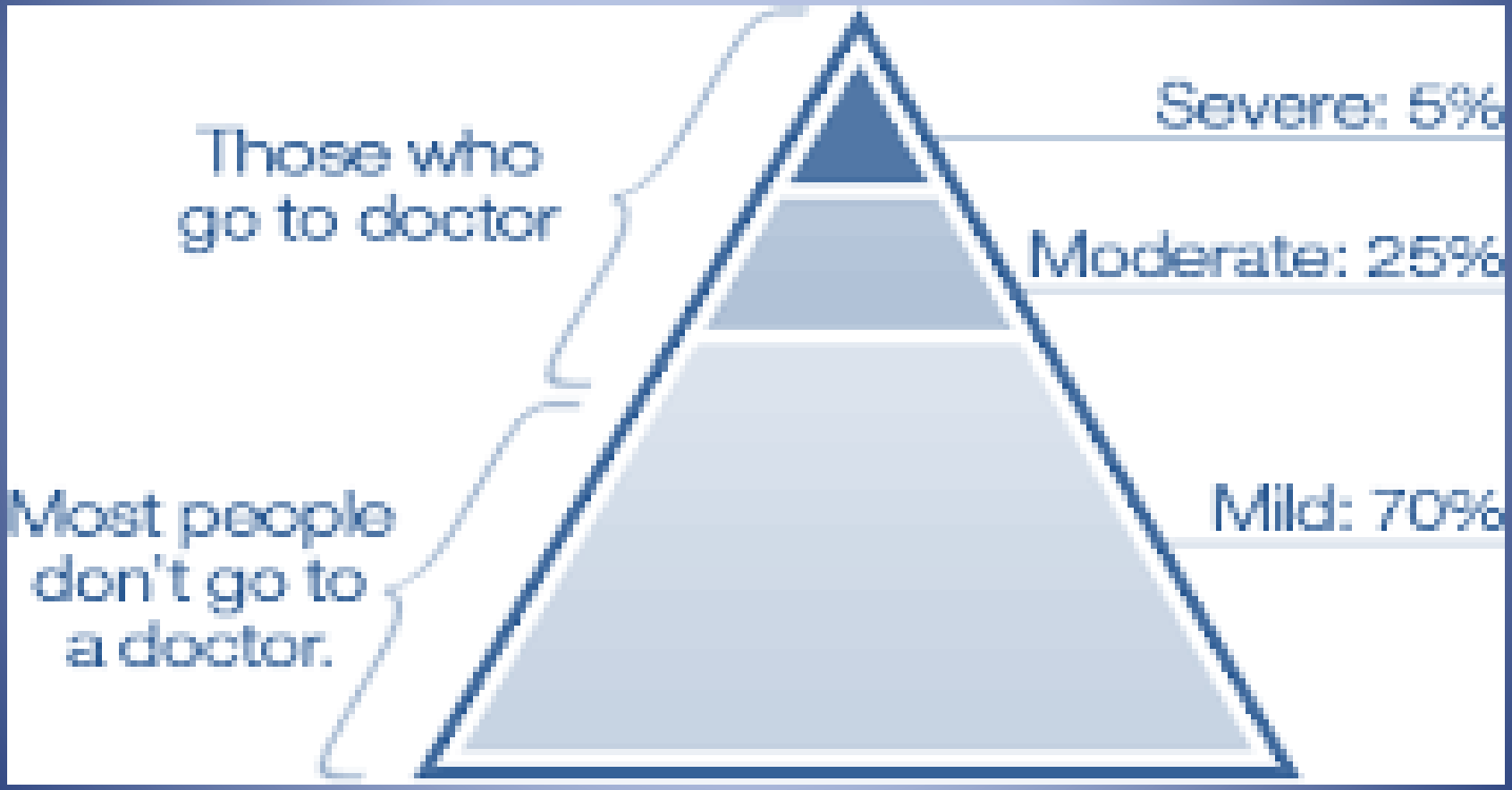
IBS Severity

- GI & Extra GI symptoms
- Degree of disability
- Illness related perceptions
- Illness related behavior
- Psychological distress

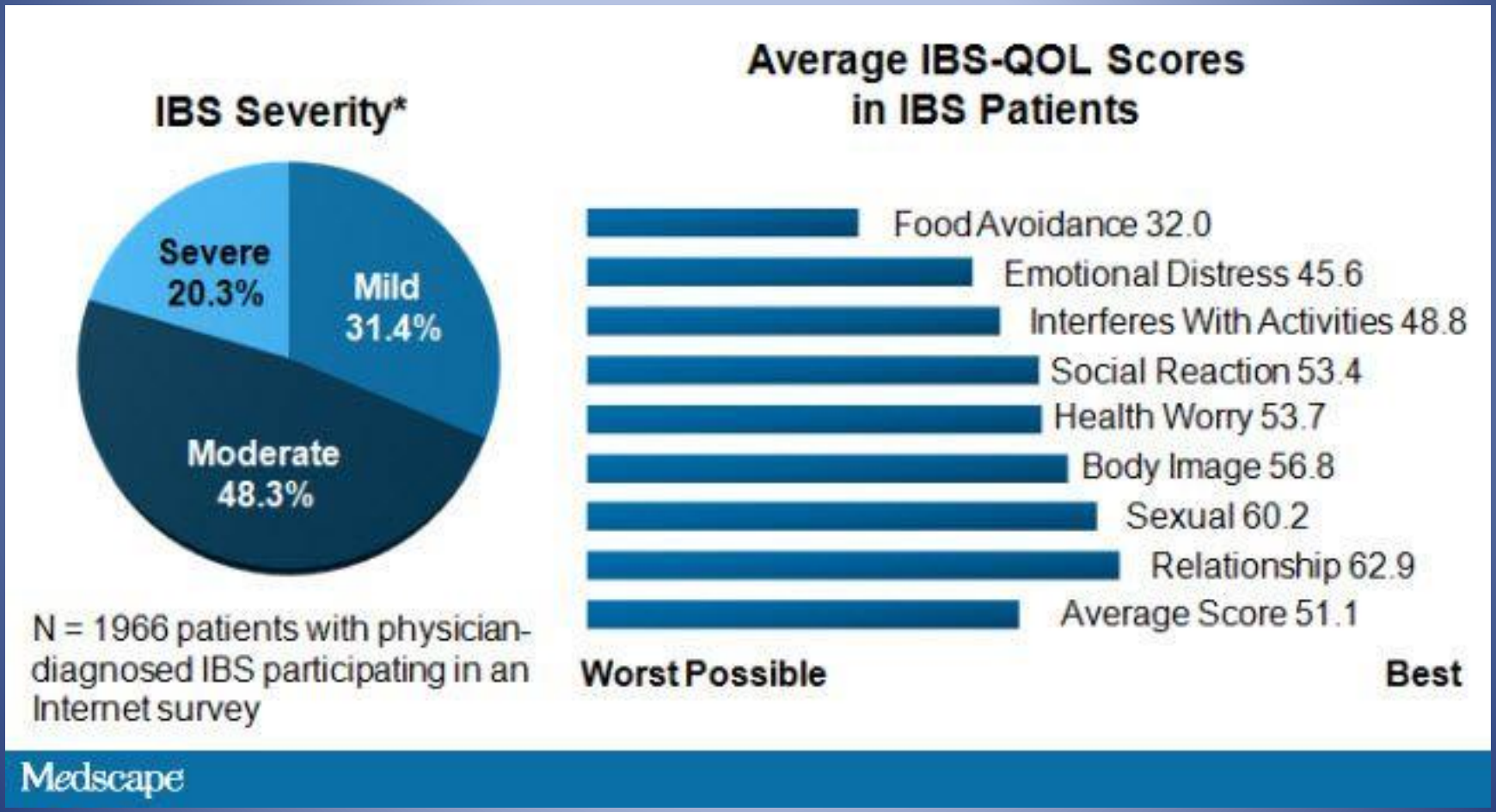


Drossman 2012

IBS Severity



Quality of life

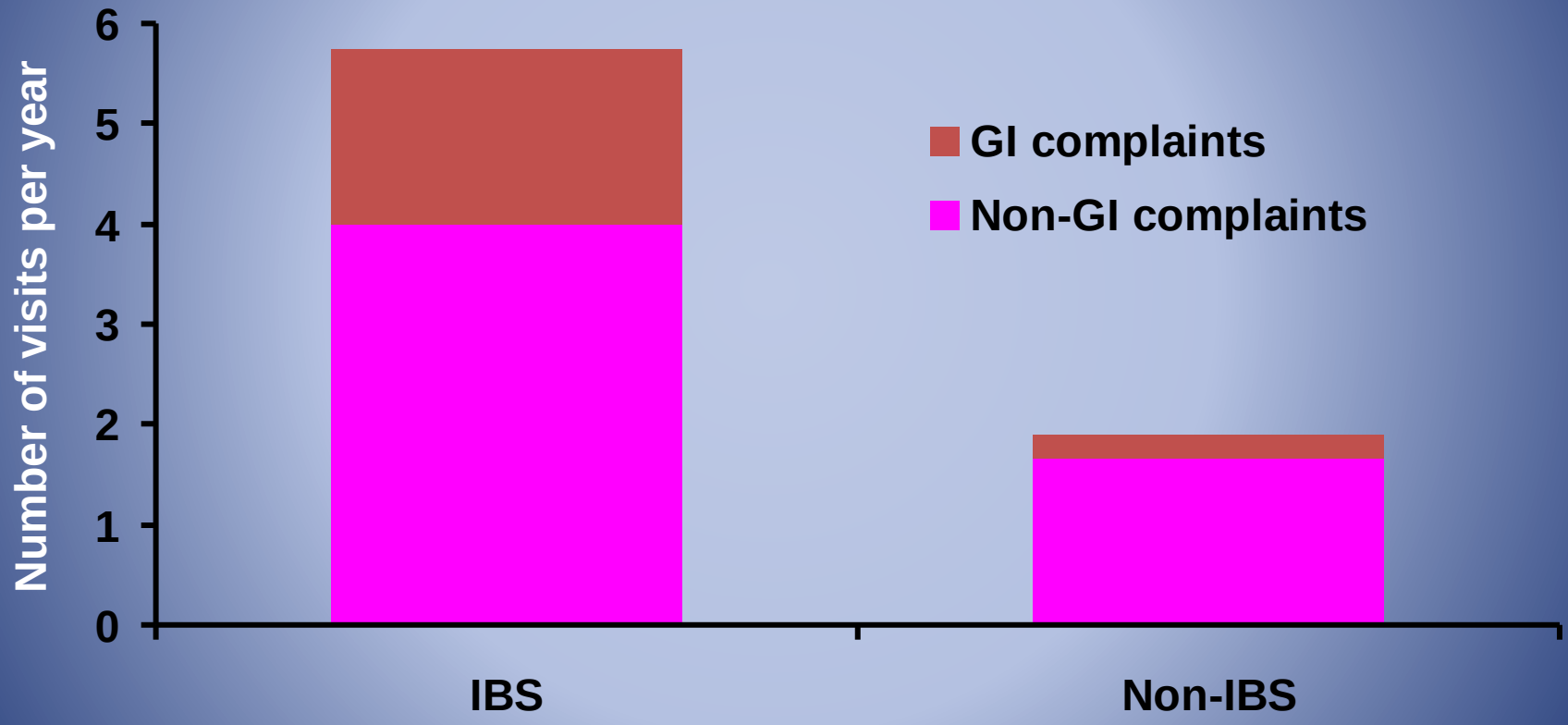


Quality of life

- **IBS patients have the same physical HRQOL as patients with diabetes, and a lower physical HRQOL compared with patients who have depression or gastroesophageal reflux disease.**

- **The health utility of severe IBS is similar to that of Class 3 congestive heart failure and rheumatoid arthritis.**

Physician visits per year

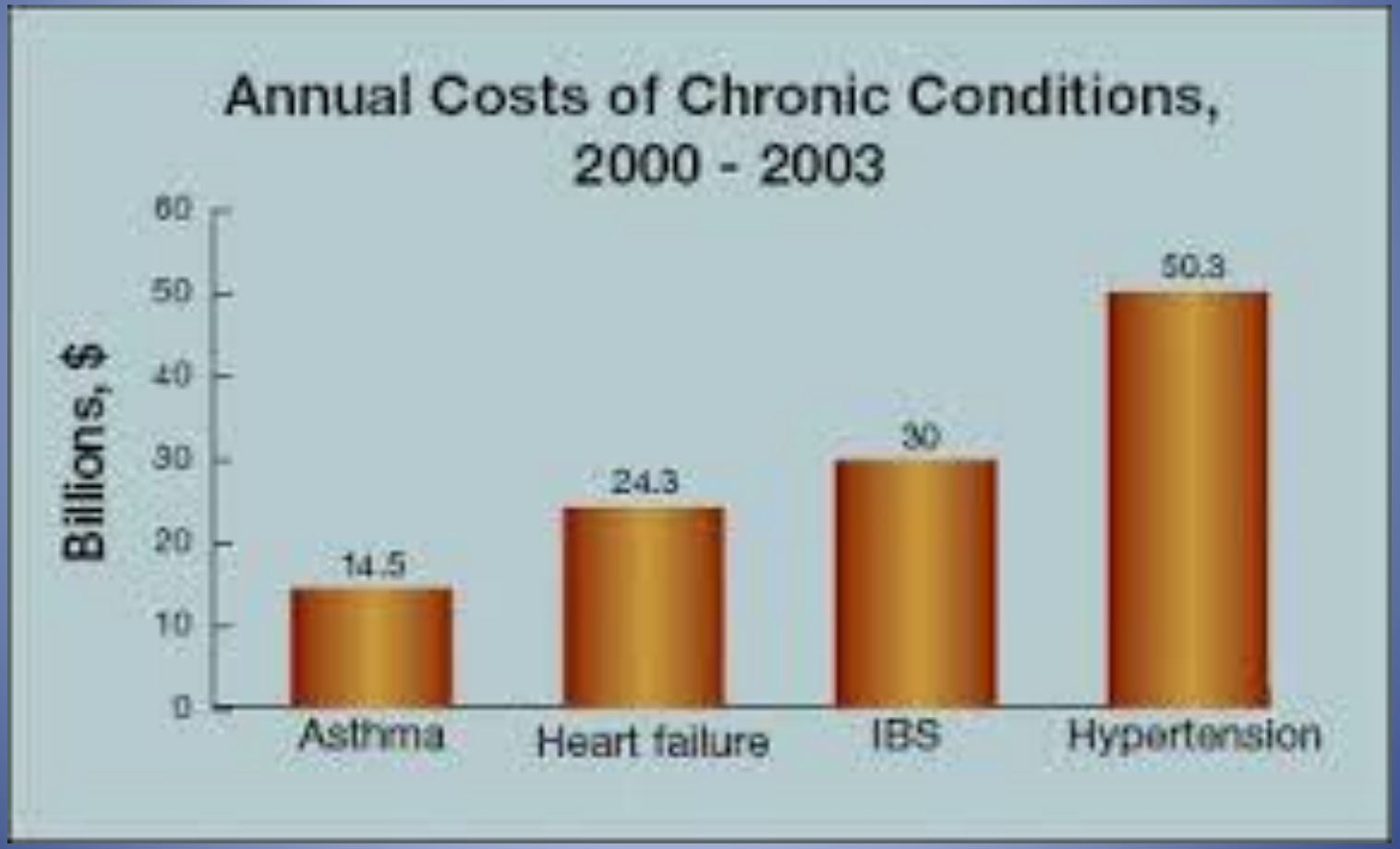


Drossman et al., 1993
AGA Teaching Unit in IBS, 1997

Essential Data on Costs in IBS

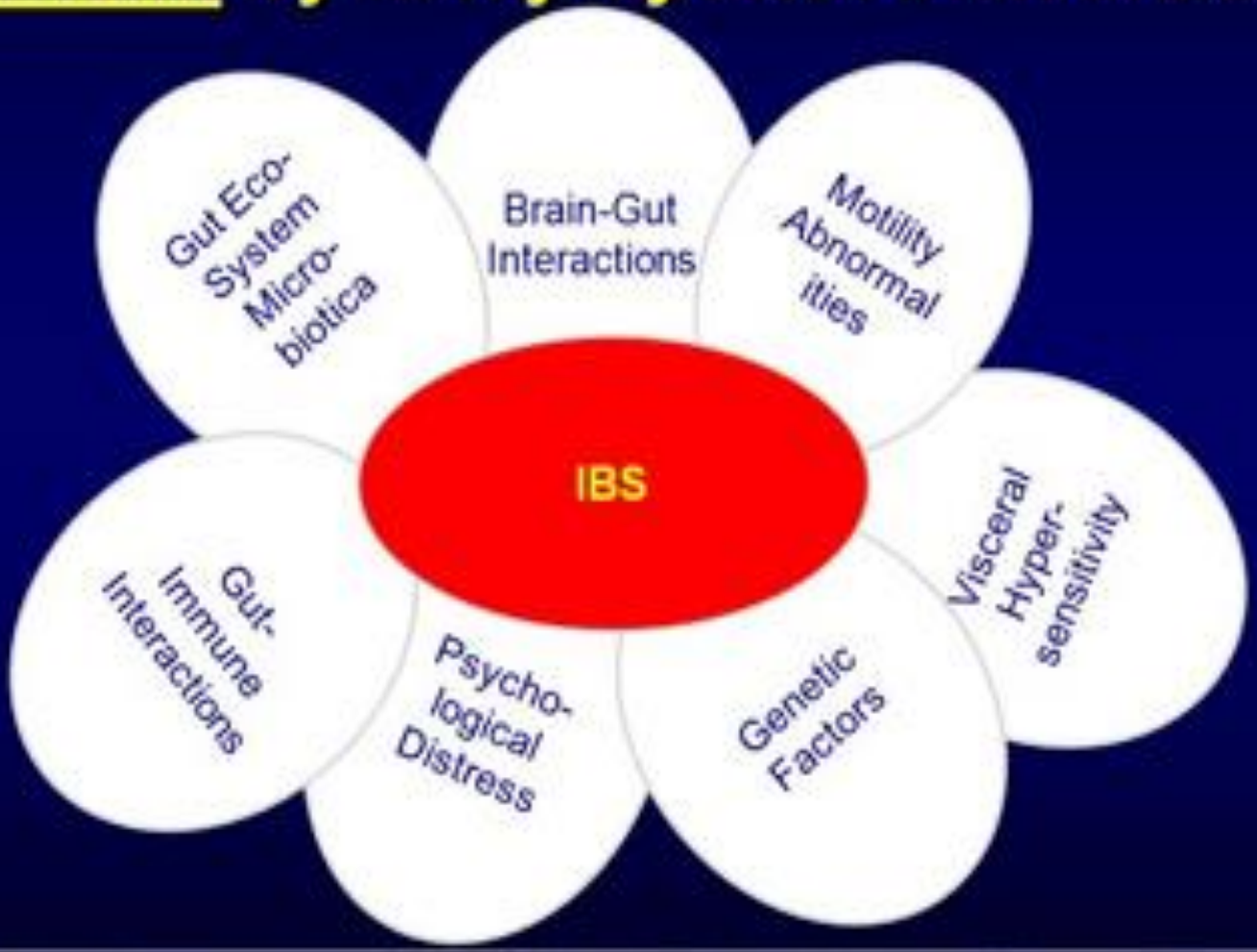
- $41 billion estimated direct and indirect costs for IBS in 8 most industrialized countries
- $25 billion in USA

- $8.4 billion direct charges in 1992.
- About 0.5% of entire health care budget


Annual Costs of Chronic Conditions, 2000 - 2003
Billions, $
60
50
40
30
20
10
0
14.5
24.3
30
50.3
Asthma
Heart failure
IBS
Hypertension

Pathophysiology

IBS is a Complex Syndrome Caused by Many System Interactions

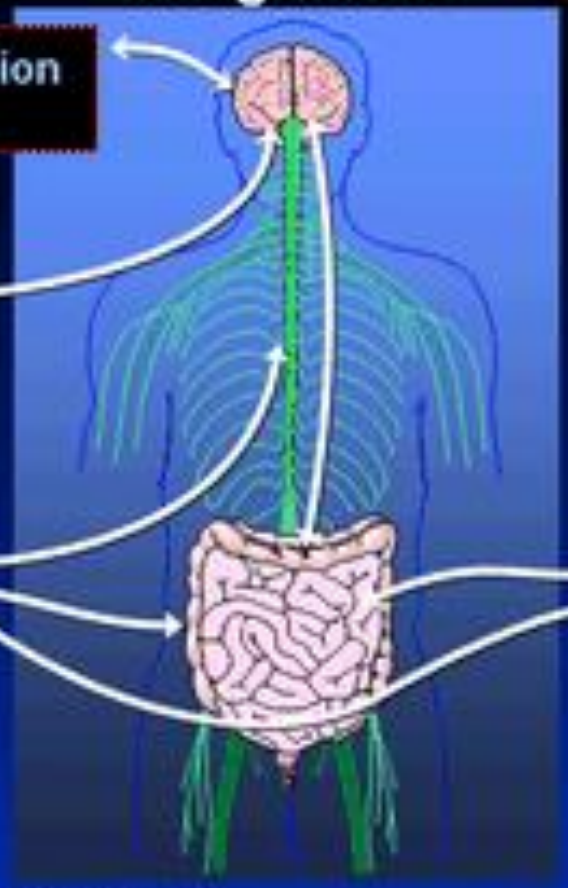


Brandt, LJ, et al. Am J Gastroenterol. 2002;97: S7–S26; Al-Khatib K et al. Gut Liver. 2009;3:14-9. Thabane M et al. W J Gastro. 2009;15:3591-6. Manabe N et al. Sm Mus Res. 2009;45:15-23. Spiller R, et al. Gut. 2007;56:1770-98. Farhadi A et al. W J Gastro. 2007;13:3027-30. Frissora CL & Cash BD. APT. 2007;25:1271-81.

Evolution of Pathophysiology in IBS

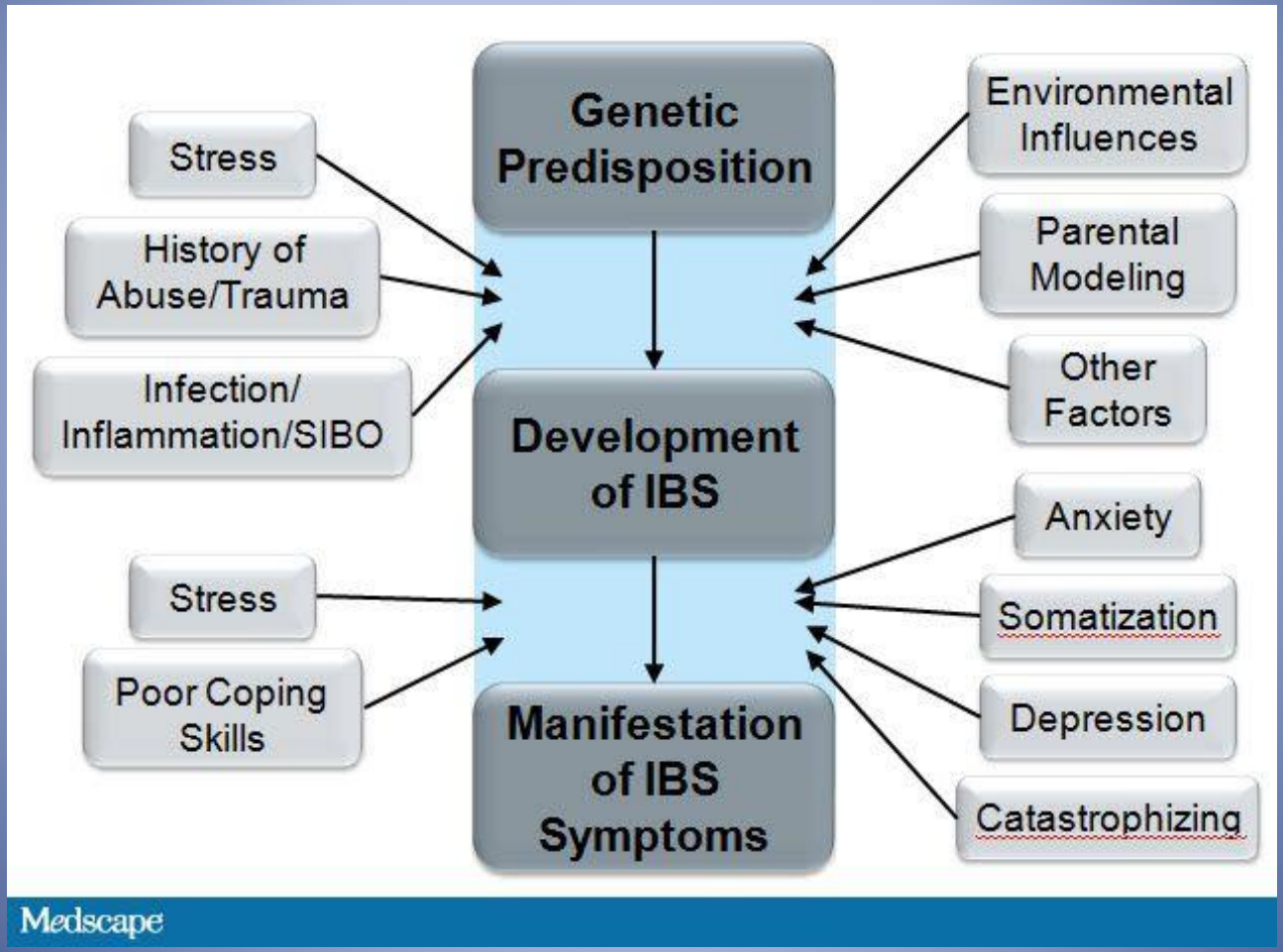
IBS - Pathophysiology

Input → Integration ← Effect

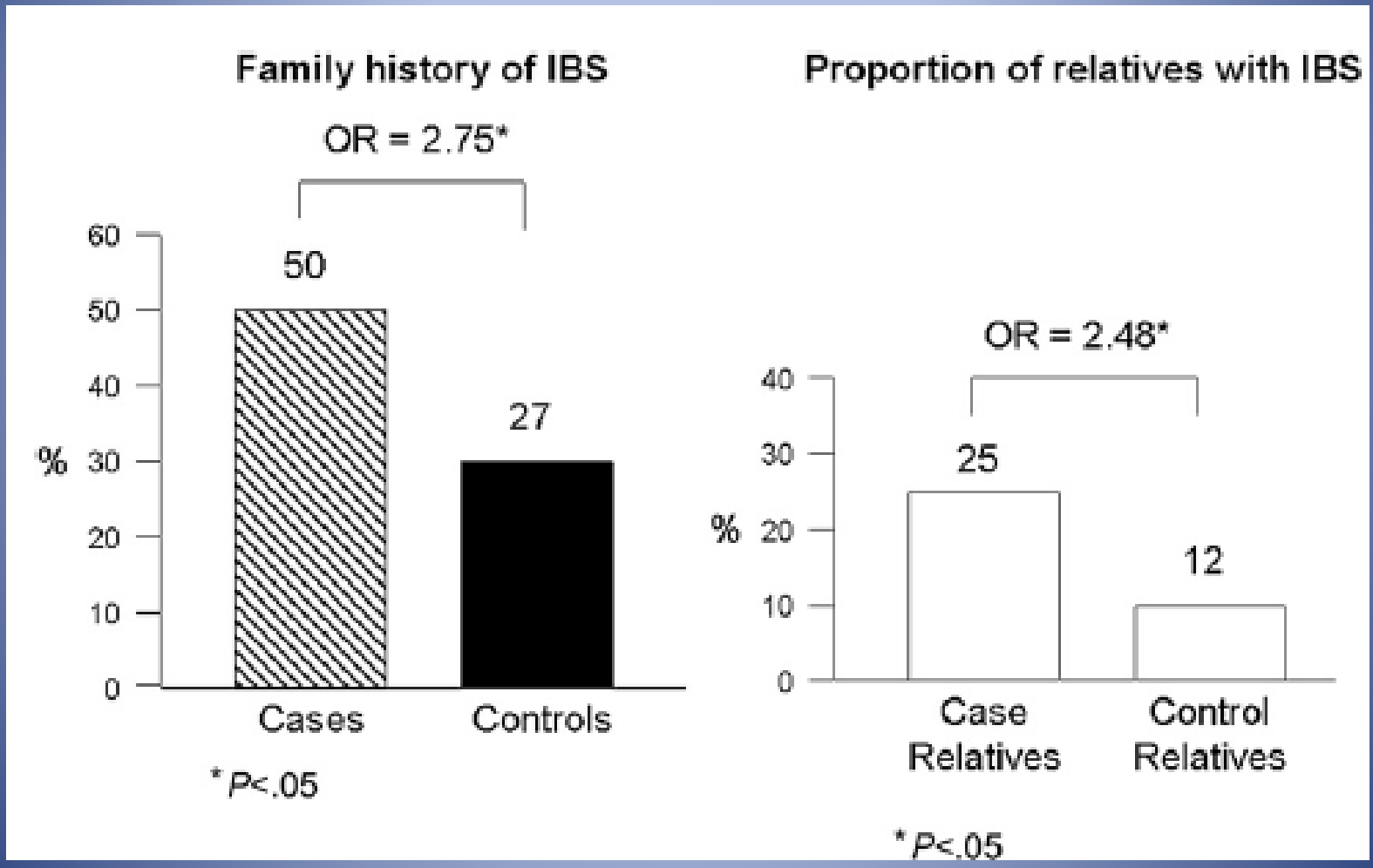


Mayer EA, Gastroenterology 1990; 99:1688

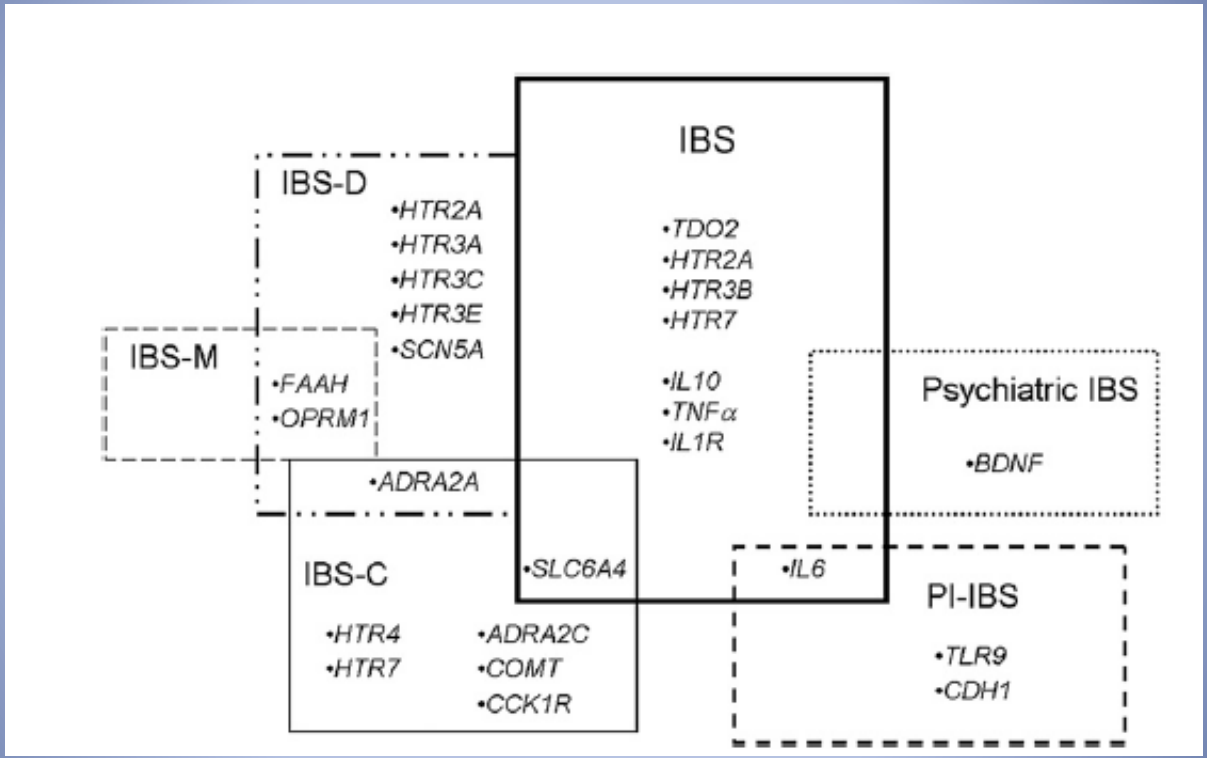
The Development of IBS



The Role of Genetics in IBS



Positive gene associations in IBS

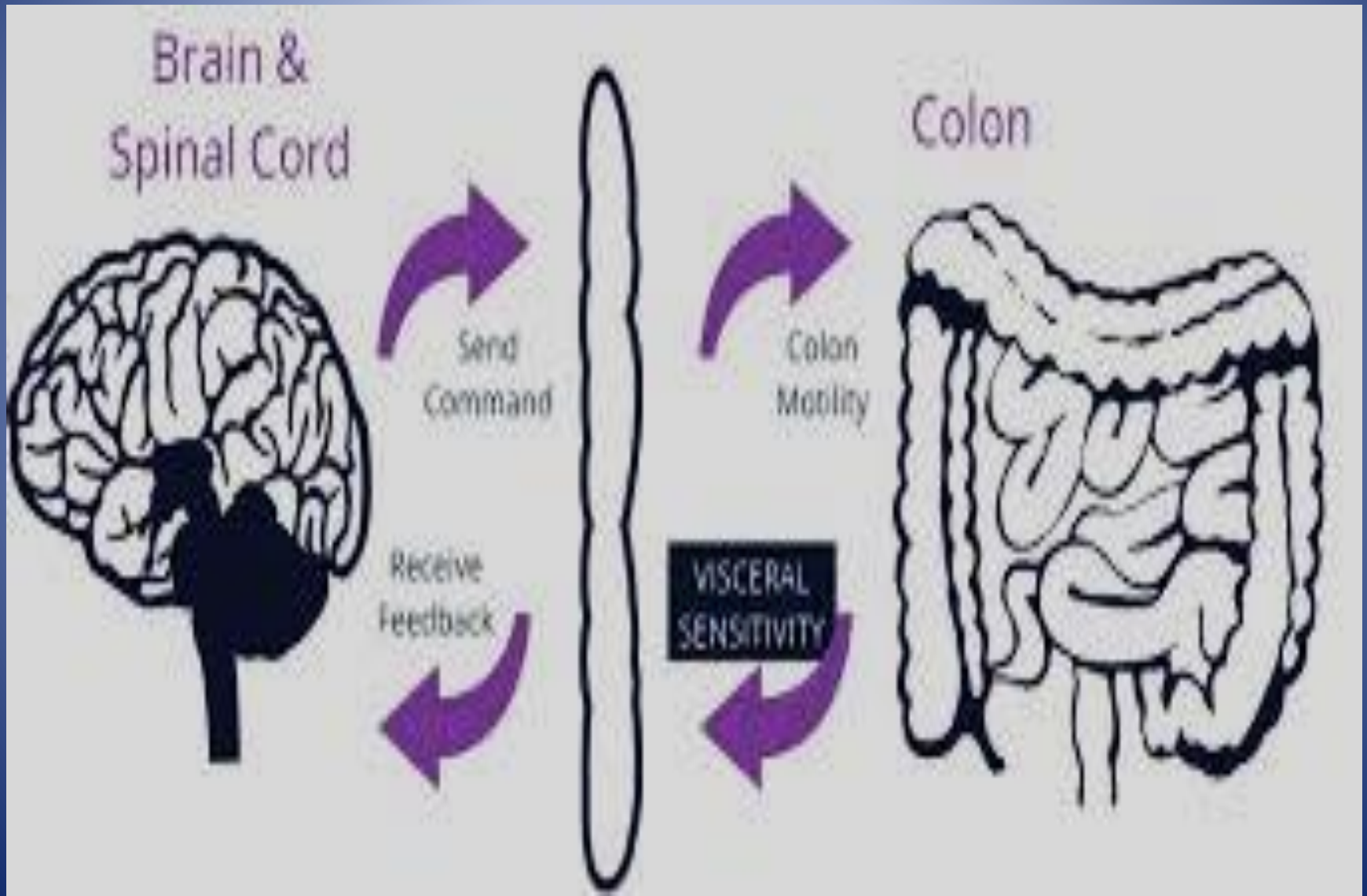


Altered visceral sensory activity

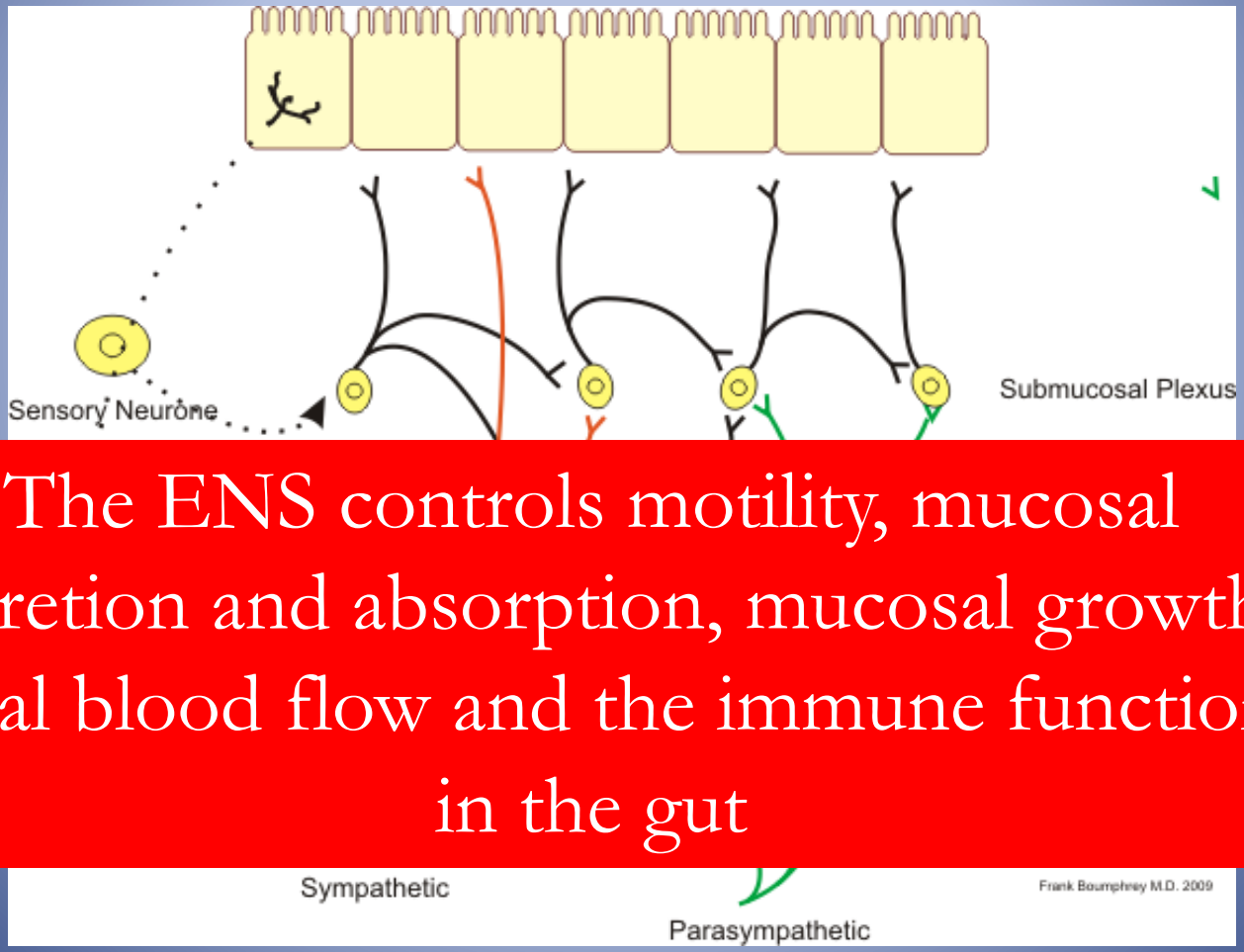
- Alterations in visceral and somatic perception are prevalent in IBS.

- Some patients with IBS experience normal physiologic events, not normally perceived by healthy individuals, as being uncomfortable or painful

Visceral Hypersensitivity

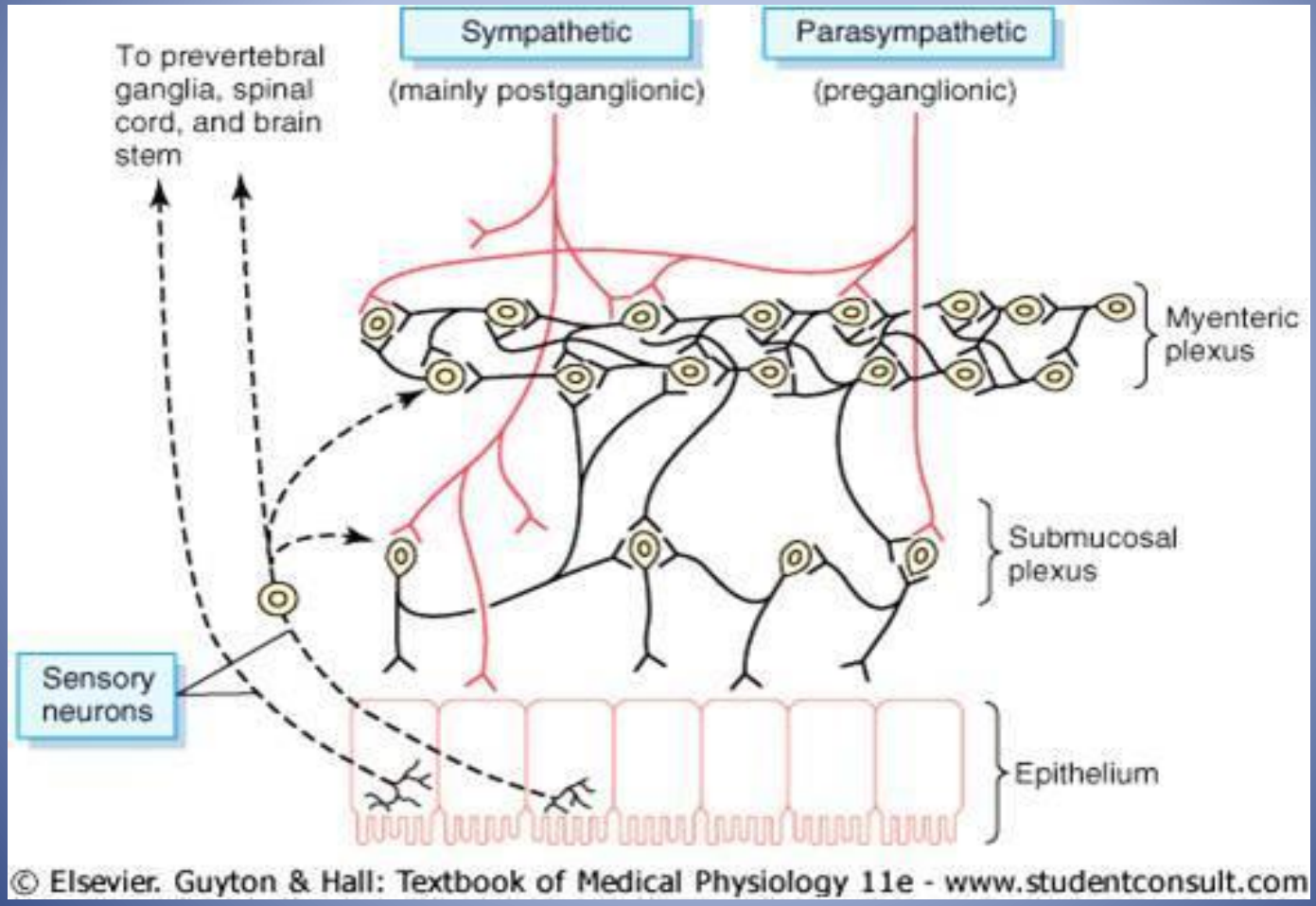


Enteric Nervous System

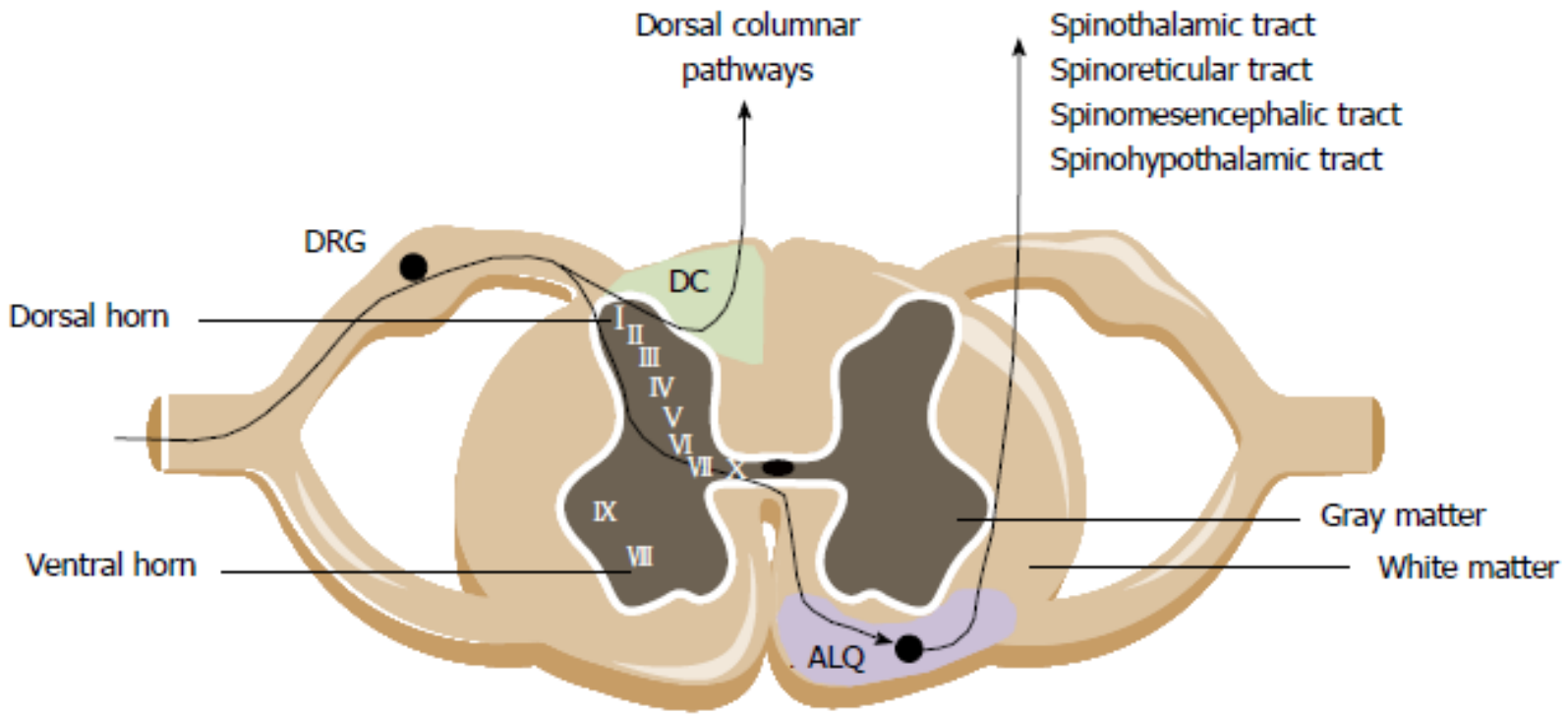


The ENS controls motility, mucosal secretion and absorption, mucosal growth, local blood flow and the immune function in the gut

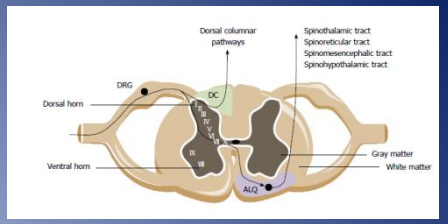
Enteric Nervous System- Extrinsic Pathways



Ascending Pathways



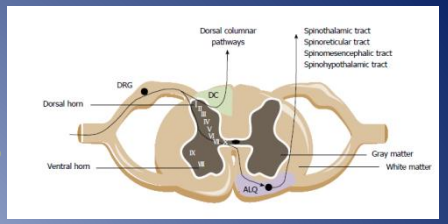
Ascending Pathways



- **The spinoreticular tract** projects to the dorsal reticular nucleus in the brainstem, which is involved in the affective-motivational properties (emotional component of pain) of visceral stimulation.

- **The spinomesencephalic tract** conveys information from the spinal cord to the periaqueductal gray and other midbrain regions.

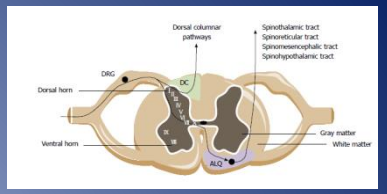
Ascending Pathways



- **The spinohypothalamic tract** conducts sensory information from the spinal cord directly to the hypothalamus.

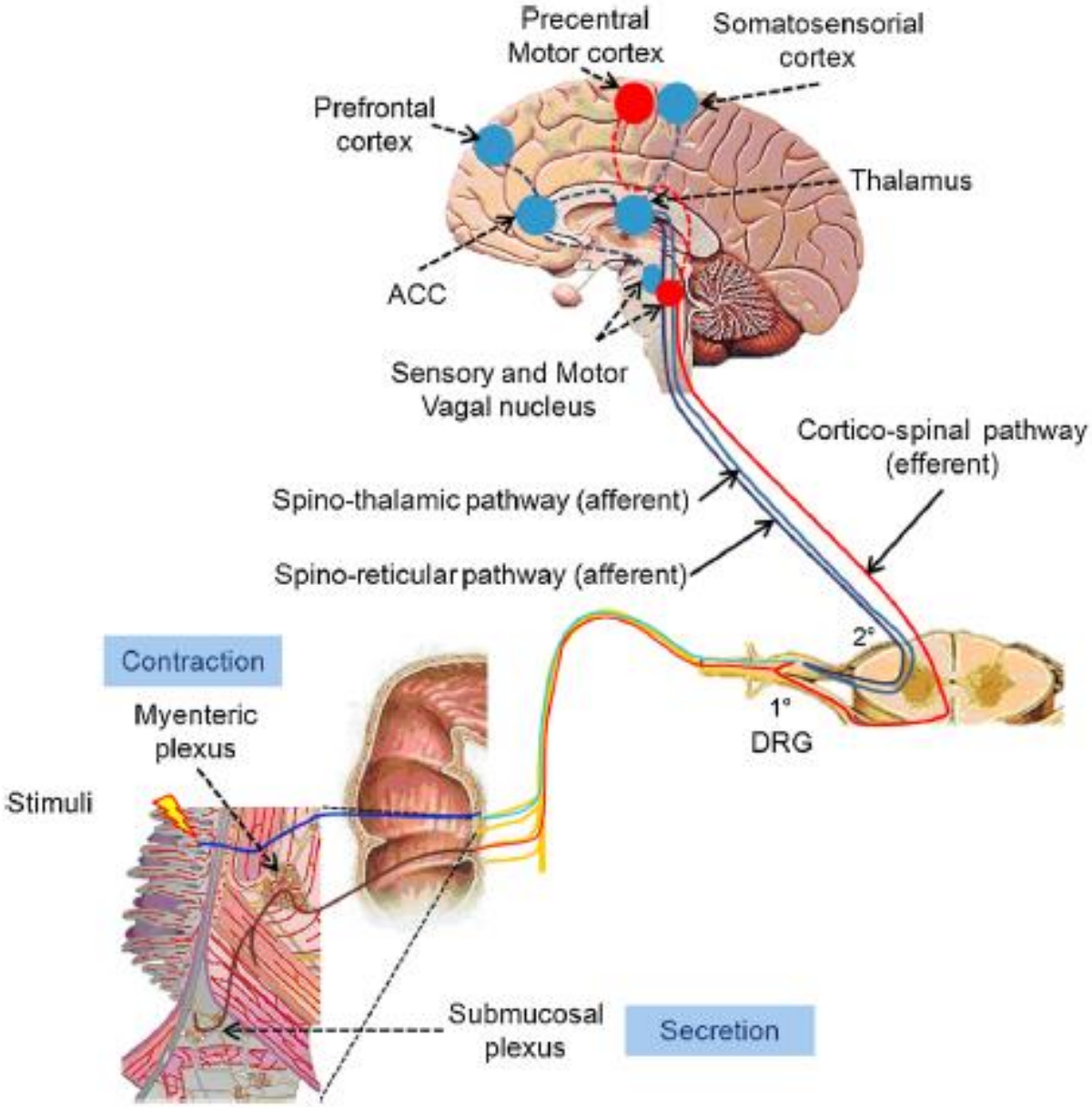
- The hypothalamus together with other parts of the limbic system (amygdala, medial thalamus, ACC), locus coeruleus and PAG regulate arousal and emotional, autonomic and behavioral responses.

Descending pathways



- Descending modulation of spinal nociceptive processing can be either inhibitory or facilitatory.

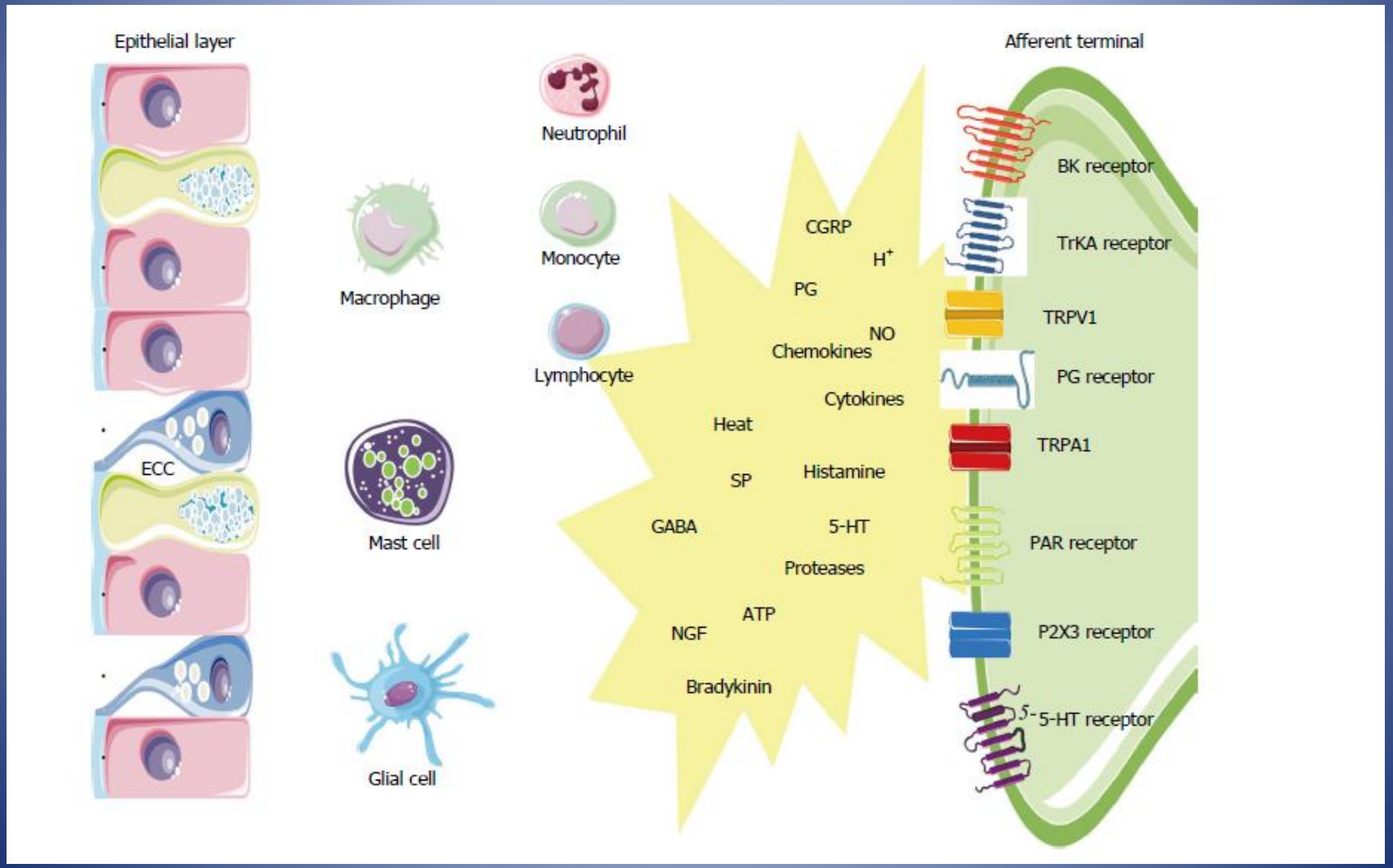
- Endogenous opioids are key mediators in the descending pain inhibitory pathways.


Precentral
Motor cortex
Somatosensorial
cortex
Prefrontal
cortex
Thalamus
ACC
Sensory and Motor
Vagal nucleus
Cortico-spinal pathway
(efferent)
Spino-thalamic pathway (afferent)
Spino-reticular pathway (afferent)
2°
1°
DRG
Contraction
Myenteric
plexus
Stimuli
Submucosal
plexus
Secretion

Mechanisms of Visceral Hypersensitivity

- ✓ Peripheral visceral afferent neurons
- ✓ Sensitization of spinal cord dorsal horn neurons
- ✓ Altered descending excitatory and inhibitory influences to the spinal cord nociceptive neurons
- ✓ Misinterpretation of innocuous sensation as noxious due to cognitive and emotional biasing (e.g., hypervigilance, pain catastrophizing)

Peripheral Sensitization

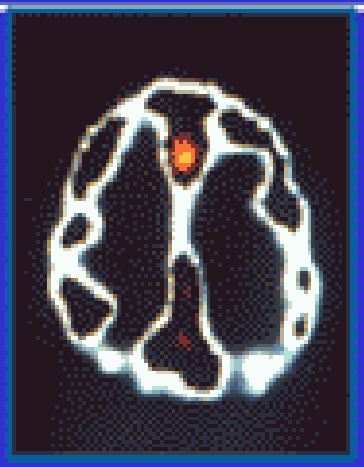


Central Sensitization

- Clinical evidence for a role of CNS sensitization in visceral pain comes from fMRI and PET studies.

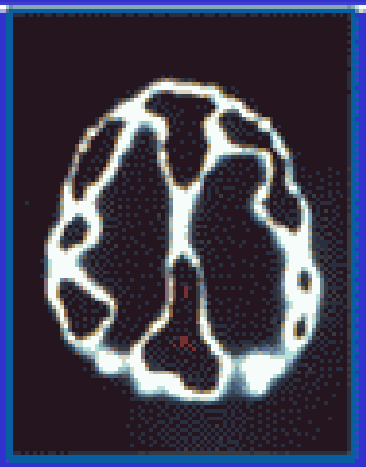
Comparison of PET Scans Showing Regional Brain Activity

Rectal distension



Anterior cingulate cortex activity

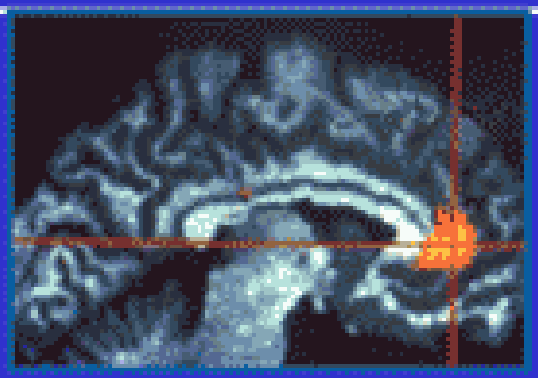
Normal



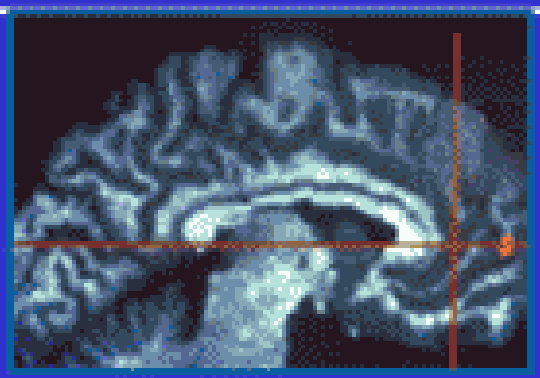
No anterior cingulate cortex activity

IBS

Anticipation of rectal distension



No prefrontal activity



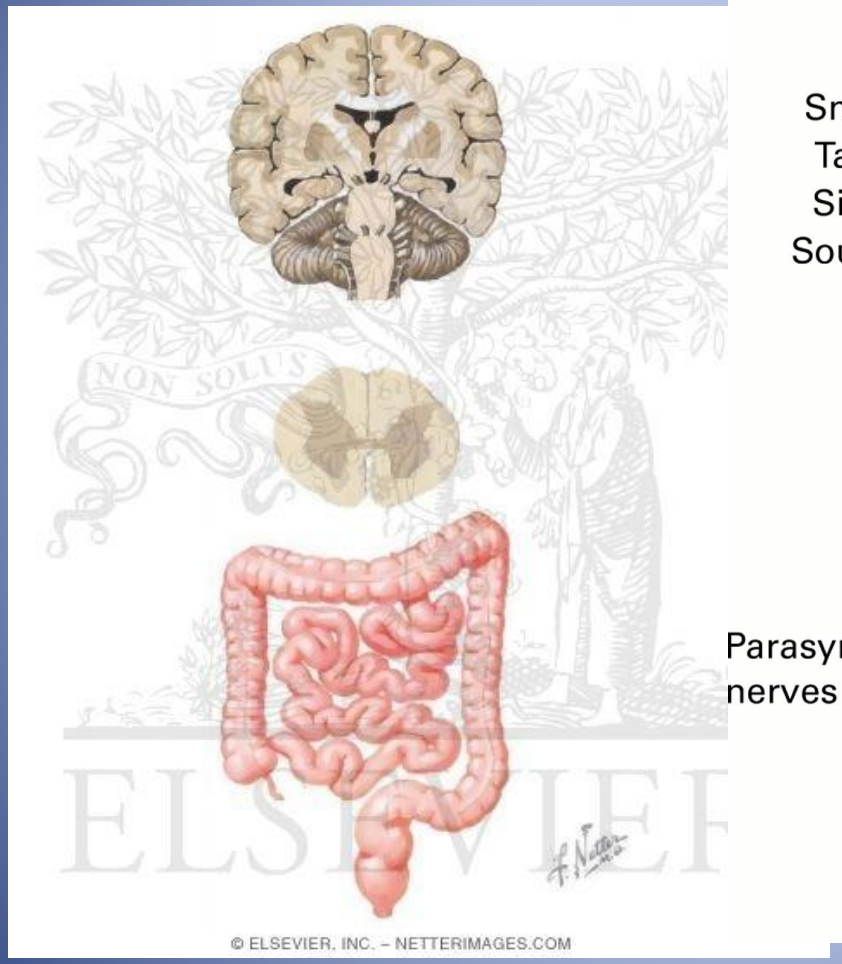
Prefrontal activity

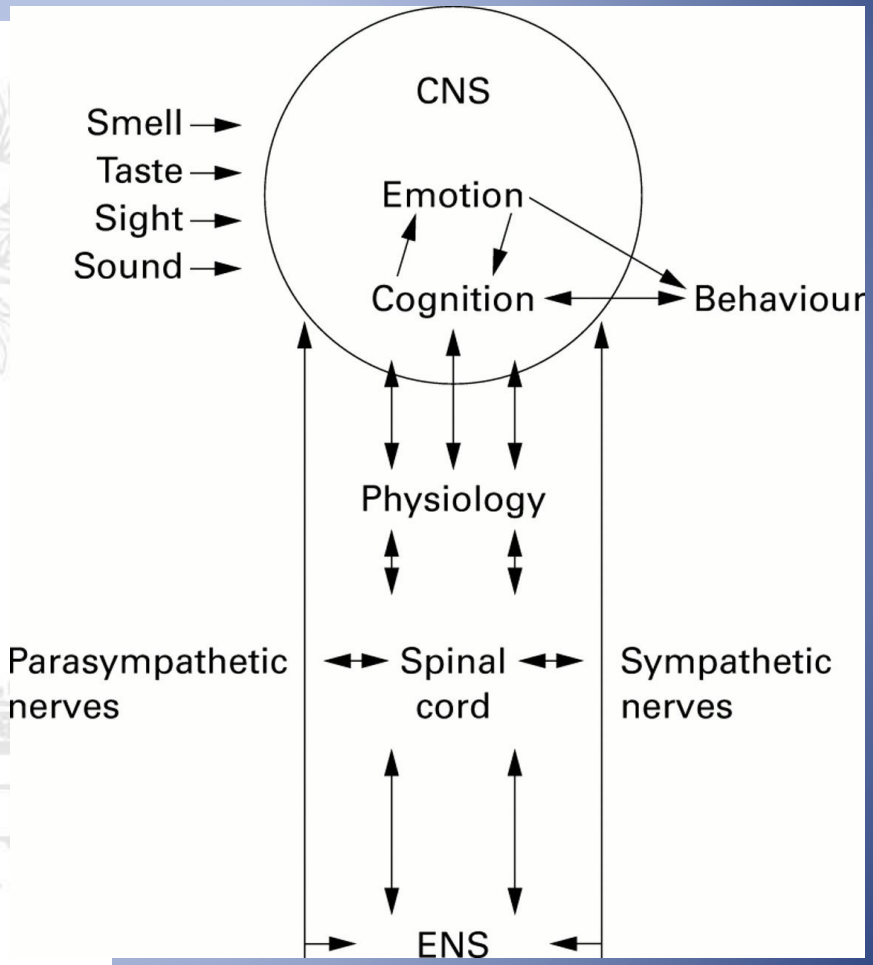
Adopted from Silverman DHS et al. *Gastroenterology*. 1997;112:64-72.

Sensitized ascending and descending pathways

- Upon repetitive stimulation by extrinsic primary afferent neurons, intracellular signaling cascades are activated within the spinal dorsal horn neurons.
- This leads to amplified responses to both innocuous and noxious input.
- Impaired ability to activate the descending pain inhibitory system.

Cognitive and Emotional Biasing





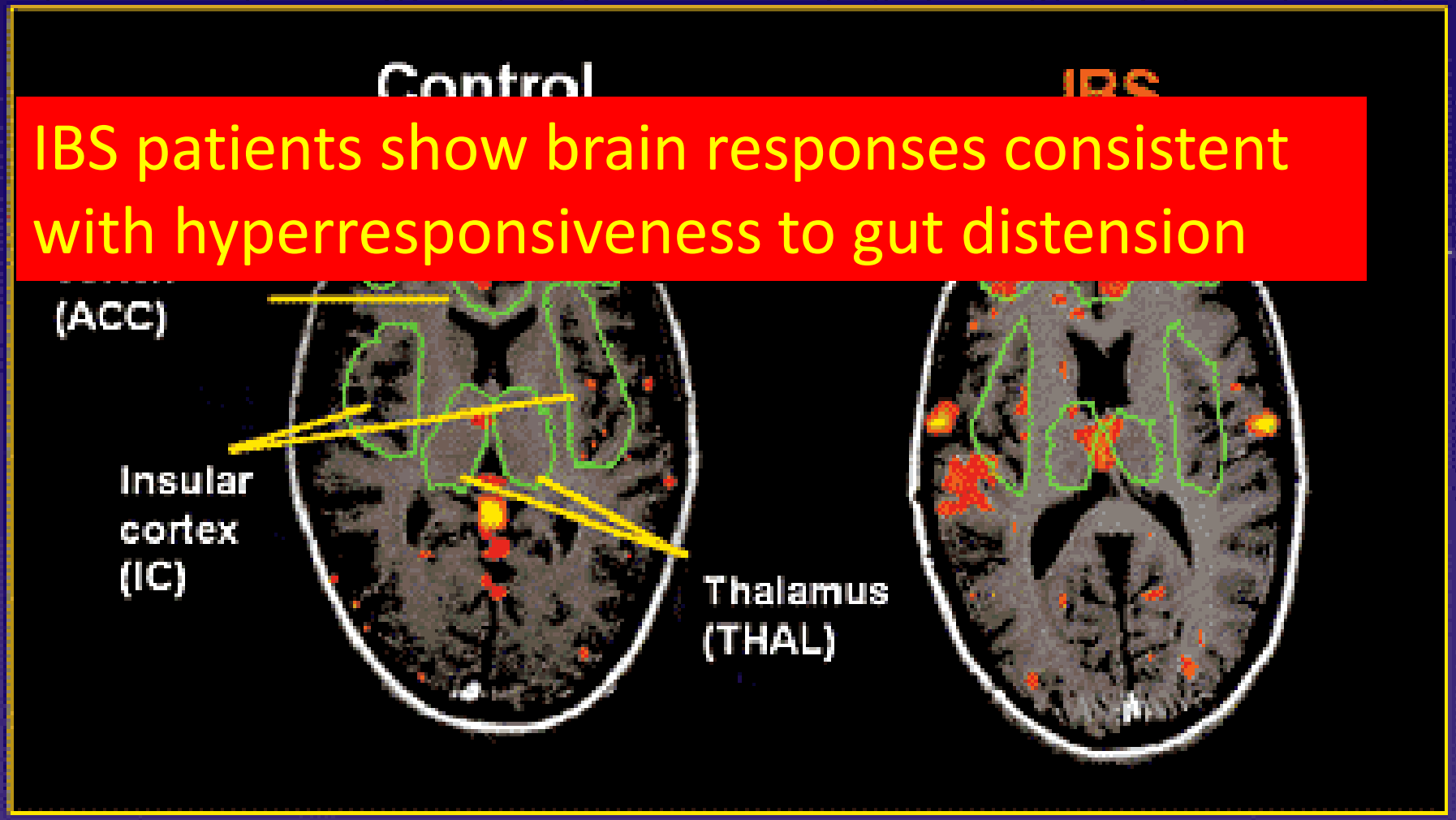
Brain-gut interactions

- CNS imaging studies have shown that IBS was associated with decreased gray matter density in various brain areas.

- Results from PET and fMRI investigations suggest that patients with IBS show significant disruptions of CNS activity related to attention, arousal, emotional, and autonomic responses to gut stimulation.

- Evoked potential recordings show results consistent with defects in visceral afferent pathways.

fMRI imaging with rectal distension in IBS

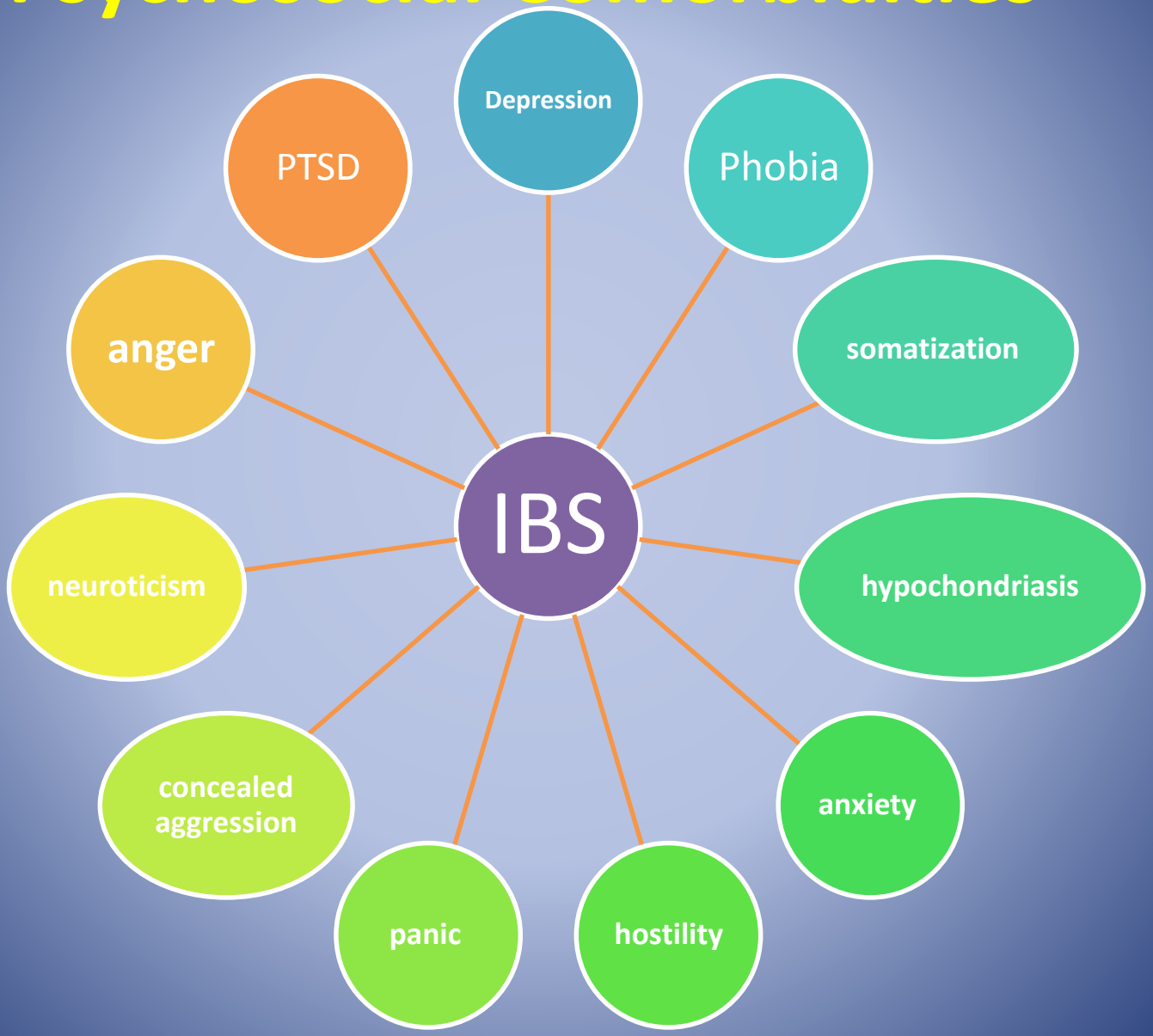


from Mertz et al, Gastroenterology 2000; 118: 842

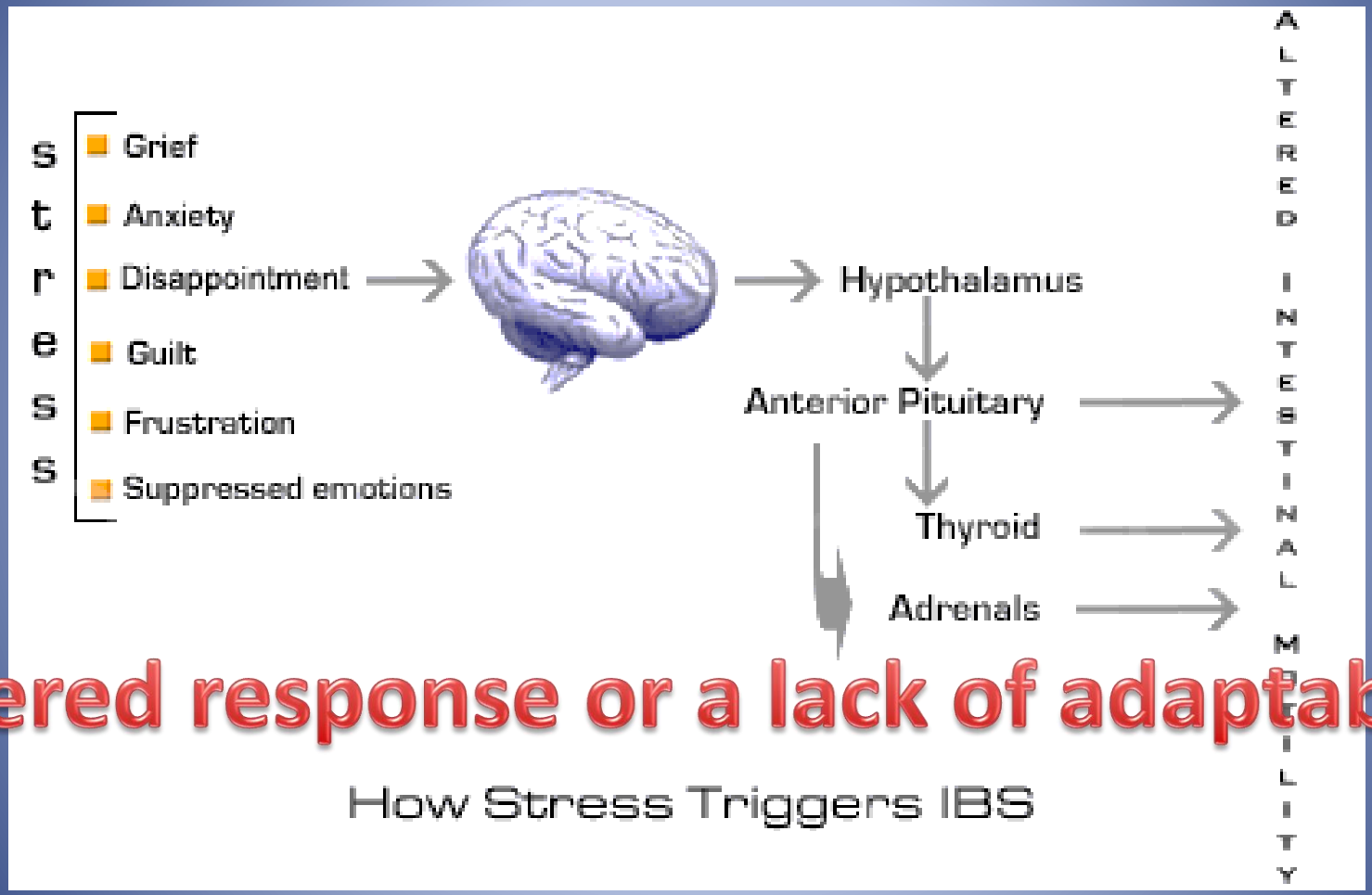
Psychosocial Distress

- Numerous studies confirm a high degree of psychosocial dysfunction in IBS.
- Psychiatric disturbances can be shown in most patients with IBS in tertiary practice, but also in patients managed in primary care and in individuals with IBS who do not seek care.
- Rates of suicidal behavior are increased 2- to 4-fold in IBS.

Psychosocial Comorbidities



Stress and IBS



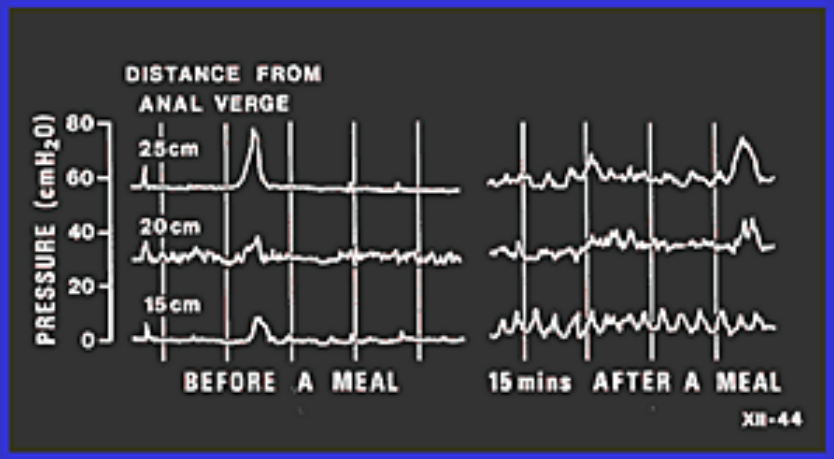
altered response or a lack of adaptability

Motor Function Disturbance

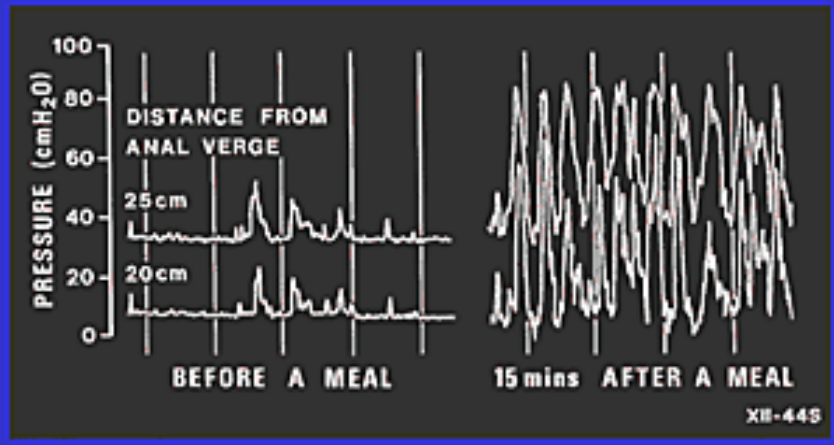
- Abnormalities of phasic small bowel contractile activity have been characterized in different subtypes of IBS.
- Colonic motor abnormalities are prevalent in IBS, but correlate imperfectly with symptomatic bowel disturbances.
- In general, colon transit is accelerated in D-IBS and delayed in C-IBS.

Pathophysiology

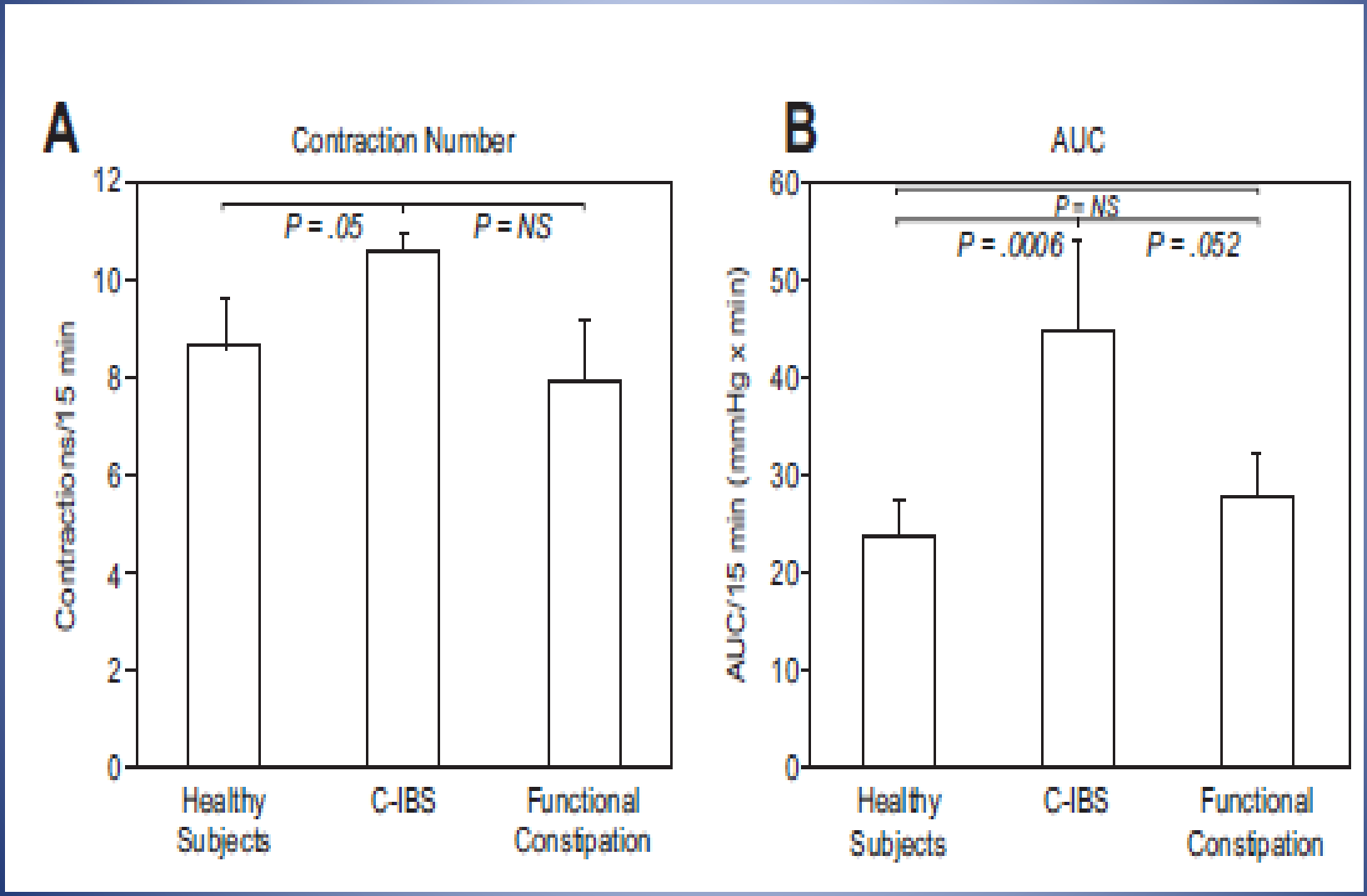
Contractions of Sigmoid Colon After a Meal (Normal Human)



Contractions of Sigmoid Colon After a Meal (Spastic Colon Syndrome)



Motor dysfunction



Inflammation

Serum and Colonic Mucosal Immune Markers in Irritable Bowel Syndrome

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OBJECTIVES: **Low-grade colonic mucosal inflammation has been postulated to have an important role in the pathophysiology of irritable bowel syndrome (IBS). The objectives of this study were (i) to identify serum and tissue-based immunological and neuroendocrine markers associated with mucosal inflammation in male (M) and female (F) patients with non-post-infectious IBS (non-PI-IBS) compared with healthy controls and (ii) to assess possible correlations of such markers with IBS symptoms.**

METHODS: **Sigmoid mucosal biopsies were obtained from 45 Rome II positive IBS patients without a history of PI-IBS (26 F, 35.5% IBS-C, 33.3% IBS-D, 31.1% IBS-A/M) and 41 healthy controls (22 F) in order to measure immunological markers (serum cytokine levels, colonic mucosal mRNA levels of cytokines, mucosal immune cell counts) and neuroendocrine markers associated with mucosal**

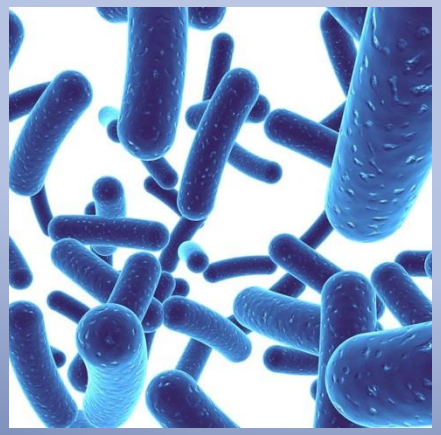
"Thus, these findings do not support that colonic mucosal inflammation consistently has a primary role in these patients".

was significantly lower (1.15±0.19 vs. 2.66±0.56, P=0.008) in female, but not male, patients compared with healthy controls. No other significant differences were observed.

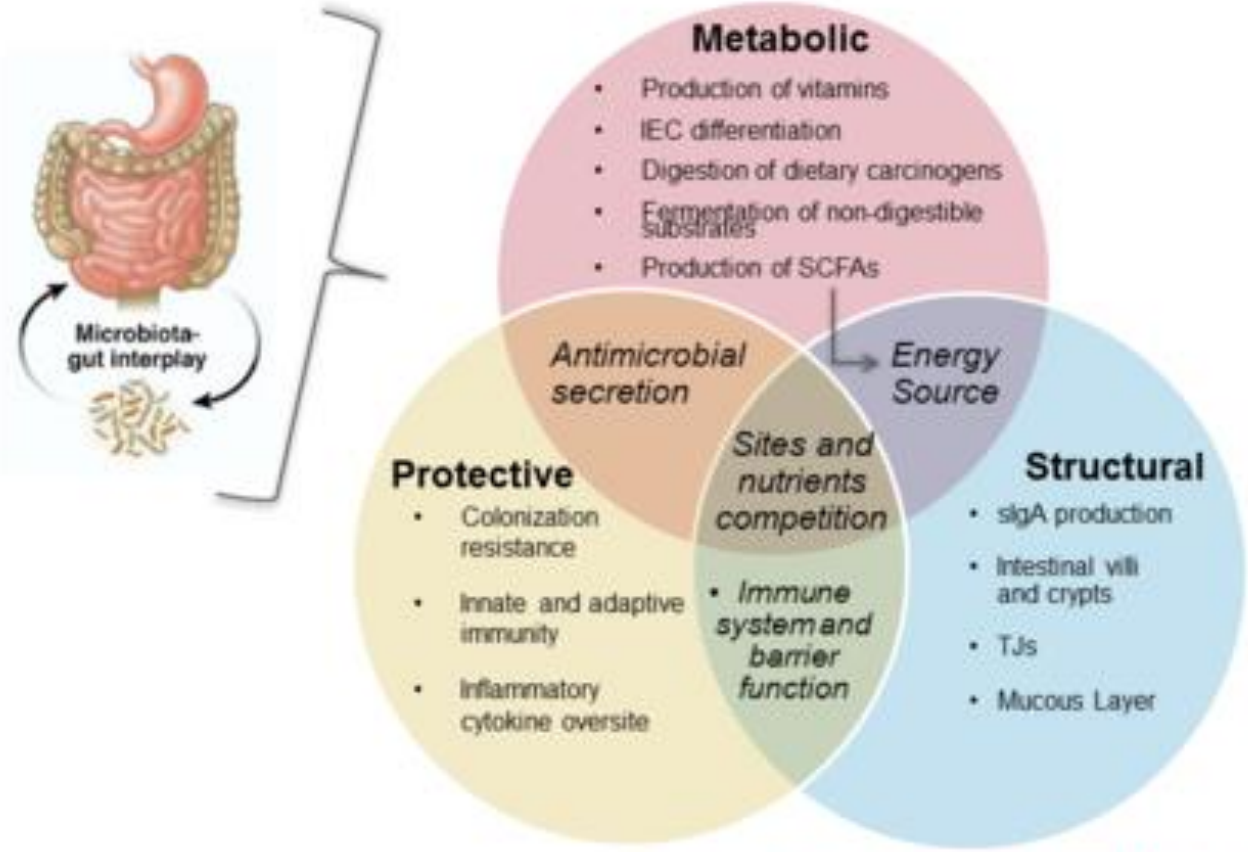
CONCLUSIONS: **Immune cell counts and levels of cytokines and neuropeptides that are associated with inflammation were not significantly elevated in the colonic mucosa of non-PI-IBS patients, and did not correlate with symptoms. Thus, these findings do not support that colonic mucosal inflammation consistently has a primary role in these patients. However, the finding of decreased IL-10 mRNA expression may be a possible biomarker of IBS and warrants further investigation.**

Microflora

- The human intestinal tract is composed of more than 500 different species of bacteria.
- There is growing evidence that supports a new hypothesis for IBS based on alterations in intestinal bacterial composition.



The Microbiota-gut Interplay Serves Many Functions



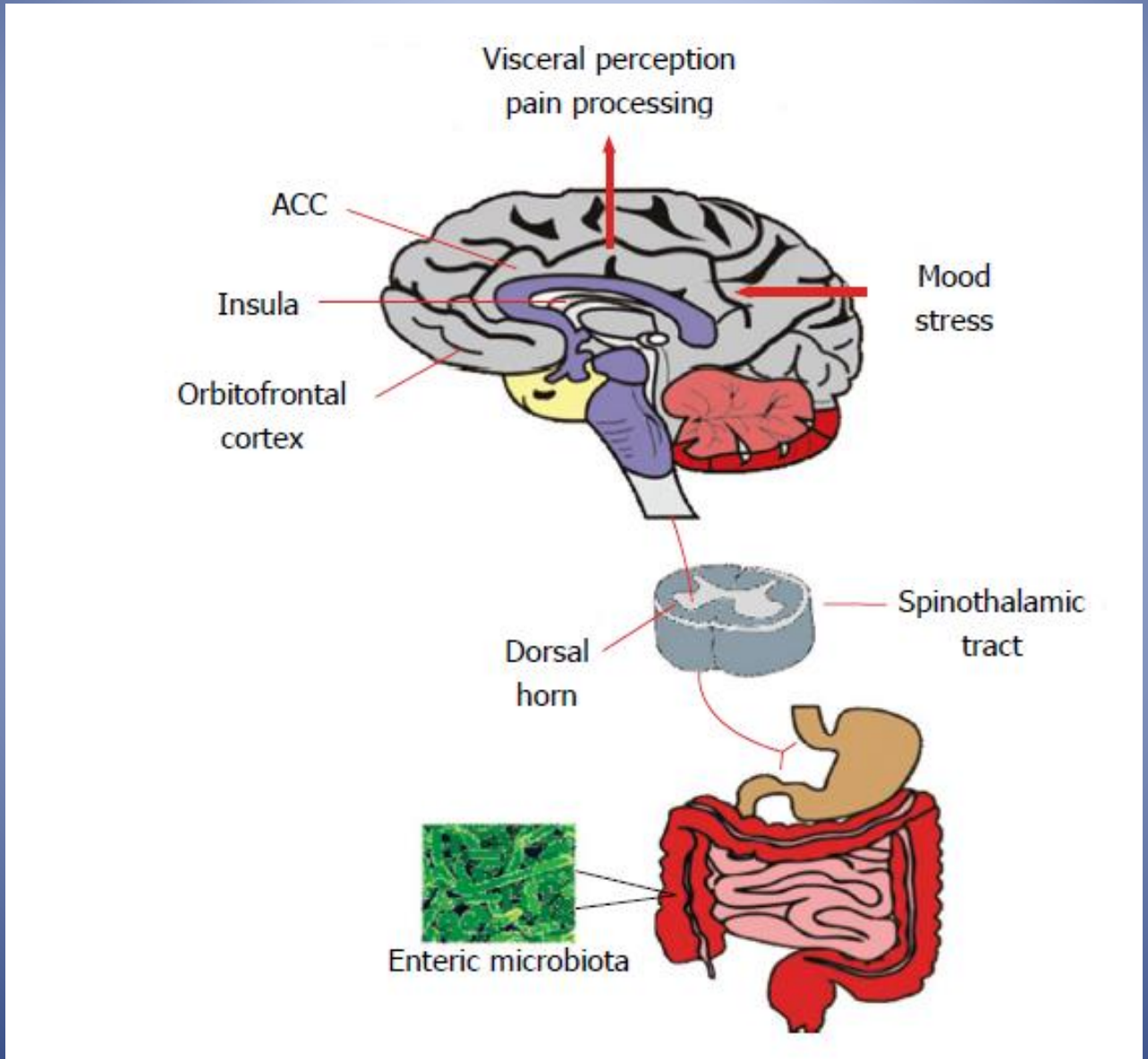
Grenham S, Clarke G, Cryan JF, Dinan TG. Brain-gut-microbe communication in health and disease. Front Physiol. 2011;2:94. Epub 2011 Dec 7. PubMed PMID: 22162969; PubMed Central PMCID: PMC3232439

Microbiota

- Gut microbiome can influence both the cardinal symptoms and other prominent features of IBS.

- The community of bacteria in IBS is less diverse and unstable.

Microbiota and Visceral pain



Microbiota Alternations in IBS

Sample type/method	Subjects recruited	Key finding	Ref.
Faecal microbiota (at 3 mo intervals)/Q-PCR (covering about 300 bacterial species)	IBS (27, Rome II Criteria; IBS-D = 12; IBS-C = 9; IBS-A = 6); Healthy Controls (22)	Decreased *Lactobacillus spp* in IBS-D; Increased Veillonella spp in IBS-C; Differences in the *Clostridium coccoides* subgroup and *Bifidobacterium catenulatum* group between IBS patients and controls	[22]
Faecal microbiota/Q-PCR (10 bacterial groups), Culture, HPLC	IBS (26, Rome II / III; IBS-D = 8; IBS-C = 11, IBS-A = 7); Healthy Controls (26)	Higher counts of *Veillonella* and *Lactobacillus* in IBS *vs* controls; Higher levels of acetic acid, propionic acid and total organic acids in IBS *vs* controls	[52]
Faecal microbiota(0, 3, 6 mo)/Culture-based techniques, PCR-DGGE analysis	IBS (26, Rome II; IBS-D = 12; IBS-C = 9; IBS-A = 5); Healthy Controls (25)	More temporal instability in IBS group; No difference in the *bacteroides, bifidobacteria*, spore-forming bacteria, *lactobacilli, enterococci* or yeasts, Slightly higher numbers of coliforms as well as an increased aerobe:anaerobe ratio in IBS group	[23]
Faecal microbiota/DNA-based PCR-DGGE, RNA-based RT-PCR-DGGE	IBS (16, Rome II; IBS-D = 7; IBS-C = 6; IBS-A = 3); Healthy Controls (16)	Higher instability of the bacterial population in IBS compared to controls; Decreased proportion of *C. coccoides-Eubacterium rectale* in IBS-C	[24]
Faecal Microbiota/GC Fractionation, 16S ribosomal RNA gene cloning and clone sequencing, qRT-PCR	IBS (24, Rome II; IBS-D = 10; IBS-C = 8; IBS-A = 6); Healthy Controls (23)	Significant differences in phylotypes belonging to the genera Coprococcus, Collinsella and Coprobacillus	[20]
Faecal Microbiota/GC Fractionation, 16S ribosomal RNA gene cloning and clone sequencing, qRT-PCR	IBS (12, Rome II, All IBS-D); Healthy Controls (22)	Significant differences between clone libraries of IBS-D patients and controls; Microbial communities of IBS-D patients enriched in *Proteobacteria* and *Firmicutes*, reduced *Actinobacteria* and *Bacteroidetes* compared to control; Greater abundance of the family *Lachnospiraceae* in IBS-D	[26]
Faecal Microbiota/qRT-PCR	IBS (20, Rome II; IBS-D = 8; IBS-C = 8; IBS-M = 4); Healthy Controls (15)	Intestinal microbiota of the IBS-D patients differed from the [illegible] groups; A phylotype with 85% similarity to *C. thermosuccinogenes* significantly different between IBS-D and [illegible]; IBS-M A phylotype with 94% similarity to R. torques more prevalent in IBS-D than controls; A phylotype with 93% similarity to *R. torques* was altered in IBS-M compared to controls; *R. bromii*-like phylotype altered in IBS-C comparison to controls	[244]
Faecal Microbiota/DGGE 16s rRNA	IBS (11, Rome II); Healthy Controls (22)	Biodiversity of the bacterial species was significantly lower in IBS than controls; presence of *B. vulgatus, B. ovatus, B. uniformis* and *Parabacteroides* sp. in healthy volunteers distinguished them from IBS	[31]
Faecal Microbiota/DGGE [illegible] rRNA, qRT-PCR GC-MS	IBS (11, Rome II; Non-IBS [illegible] (8)	IBS subjects had significantly higher diversity *Bacteroides* and *Lactobacillus* groups; Less diversity for *Bifidobacteria* and *C. coccoides*; Elevated levels of amino acids and phenolic compounds which correlated with the abundance of *Lactobacilli* and *Clostridium*	[51]
Faecal Microbiota and sigmoid colon biopsies/ DGGE 16s rRNA	IBS (47, Rome II); Healthy Controls (33)	Significant difference in mean similarity index between IBS and healthy controls; Significantly more variation in the gut microbiota of healthy volunteers than that of IBS patients	[29]
Faecal Microbiota and brush duodenal samples/FISH + qRT-PCR	IBS (41, Rome II; IBS-D = 14, IBS-C = 11; IBS-A = 16); Healthy Controls (26)	2-fold decrease in the level of bifidobacteria in IBS patients compared to healthy subjects; no major differences in other bacterial groups. At the species level, *B. catenulatum* significantly lower in IBS patients in both faecal and duodenal brush samples than in healthy subjects	[21]
Faecal Microbiota and brush duodenal samples/DGGE 16s rRNA, q-RT-PCR	IBS (37, Rome II; IBS-D = 13, IBS-C = 11; IBS-A = 13); Healthy Controls (20)	Higher levels *P. aeruginosa* in the small intestine and faeces of IBS than healthy subjects	[47]
Faecal Microbiota and colonic mucosal samples/Culture, qRT-PCR	IBS (10, Rome III, all IBS-D); Healthy Controls (10)	Significant reduction in the concentration of aerobic bacteria in faecal samples from D-IBS patients when compared to healthy controls 3.6 fold increase in concentrations of faecal *Lactobacillus* species between D-IBS and healthy controls; No significant differences were observed in the levels of aerobic or anaerobic bacteria in colonic mucosal samples between D-IBS patients healthy controls; No significant differences in mucosal samples between groups for *Clostridium, Bacteroides, Bifidobacterium* and *Lactobacillus* species and *E. coli*	[46]
Faecal Microbiota and colonic mucosal samples/T-RFLP) fingerprinting of the bacterial 16S rRNA gene	IBS (16, Rome III, All IBS-D); Healthy Controls (21)	1.2-fold lower biodiversity of microbes within faecal samples from D-IBS compared to healthy controls; No difference in biodiversity of mucosal samples between D-IBS and healthy controls	[30]

FIRMICUTES ↓

BACTEROIDETES ↑

Postinfectious IBS

- Numerous studies have shown that IBS can be precipitated by an episode of acute gastroenteritis.
- 10% of subjects who have AGE develop IBS, with a summary odds ratio of 6 to 7.
- The 2 most significant of these are duration/severity of gastroenteritis and female sex.

Antibiotic Treatment of IBS: Support for a Gut Flora Hypothesis

The NEW ENGLAND JOURNAL of MEDICINE

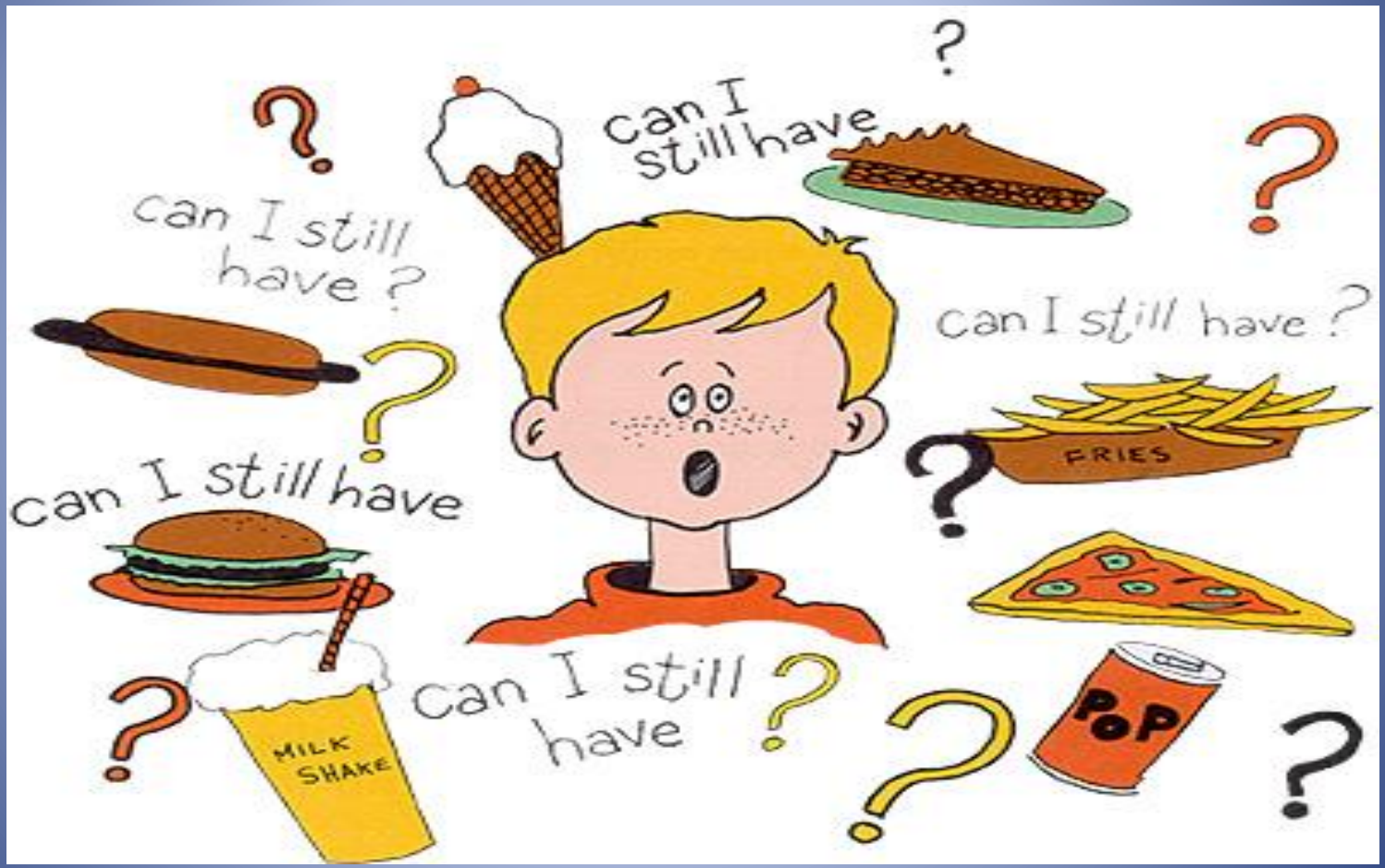
ORIGINAL ARTICLE

Rifaximin Therapy for Patients with Irritable Bowel Syndrome without Constipation

Mark Pimentel, M.D., Anthony Lembo, M.D., William D. Chey, M.D., Salam Zakko, M.D., Yehuda Ringel, M.D., Jing Yu, Ph.D., Shadreck M. Mareya, Ph.D., Audrey L. Shaw, Ph.D., Enoch Bortey, Ph.D., and William P. Forbes, Pharm.D., for the TARGET Study Group*

TARGET 1 and TARGET 2: In these studies, rifaximin was effective in improving IBS based on abdominal pain, stool consistency, bloating, and the primary outcome measure of global relief.

Food and IBS


can I still have ?
can I still have ?
can I still have ?
can I still have ?
can I still have ?
FRIES
MILK SHAKE
POP

Meal-Induced Symptoms

- More than 60% of IBS patients report worsening of symptoms after meals
- 28% of these within 15 minutes after eating
- 93% within 3 hours

- Simren M *Digestion*. 2001;63:108-115.

Food as a trigger for IBS Symptoms

- Food allergy
- Food intolerance
- Lack of fibers?
- Others

Food Allergy

Not related to IBS

Non- IgE mediated reaction

- Slower reaction
- T lymphocytes, mast cells, eosinophils involved
- Increase in mucosal eosinophils and mast cells in IBS, close association of these cells with enteric nerves in the mucosa
- Immunemediated reactions to food are probably responsible for IBS symptoms in a small proportion of adult patients with IBS.

Food Intolerance

- Lactose intolerance:
  - ✓ Does not appear to be a cause of IBS or to be more prevalent in individuals with IBS
  - ✓ Lactase supplementation did not improve IBS symptoms in a small study
- Fructose intolerance
  - ✓The effect of restricting fructose in IBS is not well established and testing for fructose malabsorption is not routinely recommended

"Wheat intolerance" and negative celiac tests

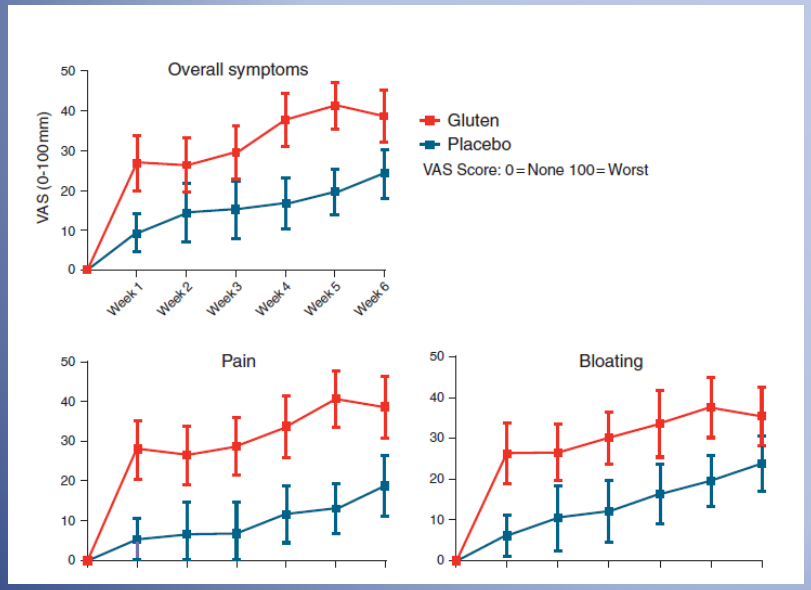
- wheat intolerance and genotype HLA DQ2 or DR3 without overt evidence of the celiac

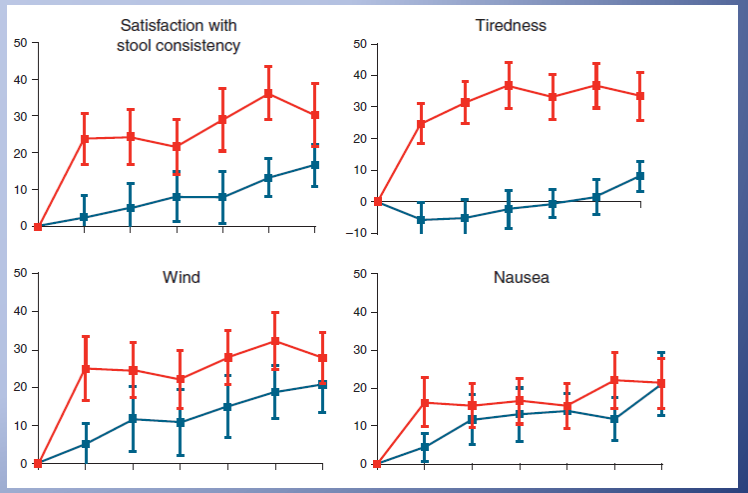
Verdu EF, Armstrong D, Murray JA. Between celiac disease and irritable bowel syndrome: the "no man's land" of gluten sensitivity. *Am J Gastroenterol* 2009; **104**: 1587–94.

Gluten Restriction

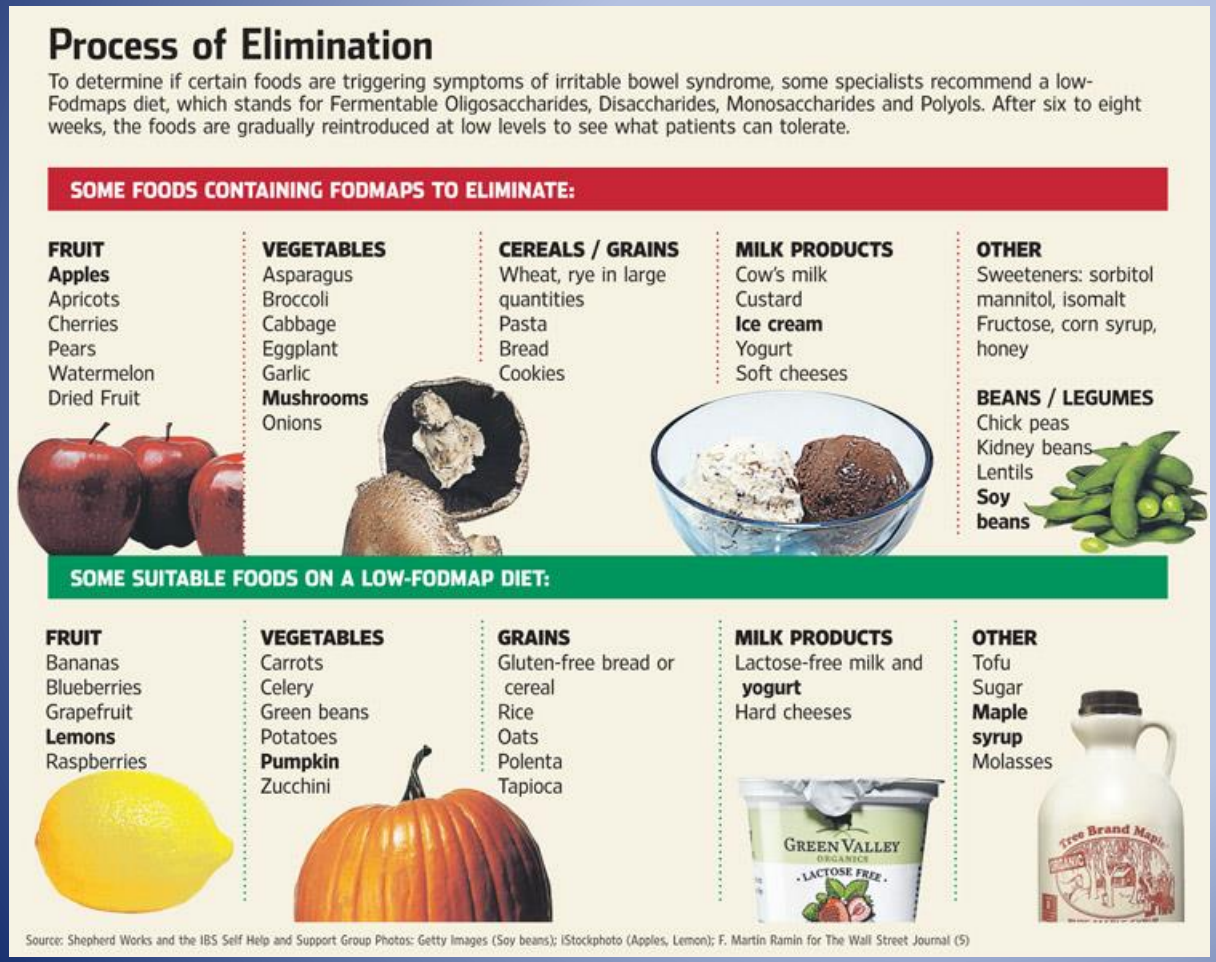
Gluten Causes Gastrointestinal Symptoms in Subjects Without Celiac Disease: A Double-Blind Randomized Placebo-Controlled Trial

Jessica R. Biesiekierski, B Appl Sci[1], Evan D. Newnham, MD, FRACP[1], Peter M. Irving, MD, MRCP[1], Jacqueline S. Barrett, PhD, BSc, MND[1], Melissa Haines, MD[1], James D. Doecke, BSc, PhD[2], Susan J. Shepherd, B Appl Sci, PhD[1], Jane G. Muir, PhD, PGrad Dip(Dietetics)[1] and Peter R. Gibson, MD, FRACP[1]





FODMAP



FODMAP restriction may be of value in some patients

Shepherd 2008

- Gas-Forming Foods :

  ✓ There is no clear evidence that IBS patients generate more gas than normal individuals, but they may be more troubled by intestinal gas

- Fat:

  ✓ The gastrocolonic motor response to lipid ingestion is exaggerated, rectal hypersensitivity is accentuated, and gas transit through the gut is delayed in response to duodenal lipid infusion

  ✓ No good clinical data

- Coffee
  - ✓Coffee stimulates gastrointestinal motility and can cause diarrhea in normal individuals
  - ✓Coffee caused a recurrence of symptoms in 14% to 33% of IBS patients on exclusion diets- within the range of placebo responses in IBS.

Therapy

Doctor- Patient Relationship

Nutritional therapy

- Avoid large meals
- Reduce lactose (eliminate milk, ice cream, and yogurt)
- Reduce fat to no more than 40 to 50 g/day
- Reduce sorbitol, mannitol, xylitol (mainly “sugarless” gum, read labels)
- Reduce fructose in all forms, including high-fructose corn syrup (read labels), honey, and high-fructose fruits (eg, dates, oranges, cherries, apples, and pears)
- Reduce gas-producing foods (eg, beans, peas, broccoli, cabbage, and bran)
- Eliminate all wheat and wheat-containing products
- A diet low in fermentable oligo-, di-, and monosaccharides and polyols (see reference 139)
- Eliminate wheat, banana, corn, potato, milk, eggs, peas, and coffee

Heizer WD J Am Diet Assoc. 2009;109:1204-1214.

FODMAP

- Low-FODMAP diets have been shown to reduce GI symptoms .

- The low-FODMAP diet also was associated with significantly lower scores for bloating, flatulence, and abdominal pain.

Table 3 | Trials examining the FODMAP-restricted diet in IBS

Study and clinical setting	IBS criteria	Methodology	Methodology Score*	Active intervention / duration	No. in FODMAP-restricted Arm	Treatment effect in FRD Arm	No. in control arm	Treatment effect in control arm	In favor of FODMAP-restriction/Significance
Ong *et al.*[58], secondary care out-patient† setting (Australia)	Rome II, IBS subtyped in to IBS-D, IBS-C, IBS-M and IBS-U	Randomised single-blind cross-over study	2/0/0 = 2	FRD (9 g)/high (50 g) FODMAP/ 2 days per diet	15	Median composite score of 2/9 (range 0–7) on Likert scale for abdominal pain, bloating and wind	15	Median composite score of 6/9 (range 2–9) on Likert scale for abdominal pain, bloating and wind	Yes, $P = 0.002$ (No subtype analysis done)
Staudacher *et al.*[59], primary/secondary care out-patient setting (UK)	NICE Guidelines, IBS subtype not reported	Non-randomised retrospective observational	0/0/0 = 0	FRD/NICE dietary guidelines (fibre, probiotics, exclusion diets) /2–6 months	43	% symptom improvement: bloating in 82%, abdominal pain 85%, gas 85%, diarrhoea 83%, constipation 67%, nausea 67%, increased energy levels 63%, composite score 86%, % satisfied with BM 76%	39	% symptom improvement: bloating 49%, abdominal pain 61%, gas in 50%, diarrhoea 62%, constipation 45%, nausea 29%, increased energy levels 37%, Composite score 49%, % satisfied with BM 54%	Yes, all symptoms improved, $P < 0.05$, except constipation and diarrhoea
de Roest *et al.*[64], secondary care out-patient† setting (New Zealand)	Not specified	Non-randomised prospective observational	0/0/1 = 1	FRD instruction from a dietitian. No control group	90	GI symptom score (7 point Likert) at baseline/6 weeks showed improvement in	NA	NA	Yes, all symptoms improved, $P < 0.05$, except feeling full long after meals, burping and passage of mucus
Bassiekierski *et al.*[60], primary/secondary care out-patient setting (Australia)						period compared with baseline, $P < 0.0001$, but not nausea ($P = 0.149$).			Yes, all symptoms improved, $P < 0.001$, except changes in nausea not significant, $P = 0.149$
Halmos *et al.*[61], secondary care out-patient† setting (Australia)	Rome II, IBS subtyped in to IBS-D, IBS-C, IBS-M and IBS-U	Randomised controlled single-blind cross-over	2/0/1 = 3	FRD (3.05 g/day)/ Control diet = average of 23.7 g FODMAP per day/ 21 days per diet	30	All IBS VAS, bloating 24.2, abdominal pain 22.5, dissatisfaction with stool consistency 25.9, composite score 73.1; similar for IBS-D and C	30	On VAS, bloating 45.1, abdominal pain 43.8, dissatisfaction with stool consistency 47.8, Composite score 137; similar for IBS-D and C	Yes, overall IBS, $P < 0.001$; similar for IBS-D and C
Pedersen *et al.*[63], out-patient, secondary care out-patient† setting (Denmark)	Rome II, IBS subtyped in to IBS-D, IBS-C, IBS-A	Randomised, unblinded controlled trial	2/0/1 = 3	FRD vs. LGG vs. ND/6 weeks	42	All IBS reduction in IBS-SSS 133 ± 122; IBS-D total IBS-SSS 153 ± 136; IBS-C total IBS-SSS 200 ± 62; IBS-A 241 ± 11; change in IBS-QOL 8 ± 18	40 ND arm	All IBS reduction in IBS-SSS 68 ± 107; IBS-D total IBS-SSS 257 ± 118; IBS-C total IBS-SSS 277 ± 126; IBS-A 322 ± 62; change in IBS-QOL 0.1 ± 15	Yes for All IBS with IBS-SSS, $P < 0.001$, IBS-D, $p < 0.01$, IBS-A, $P = 0.01$; IBS-C subtype not significant, $P < 0.14$. Change in IBS-QOL not significant in all IBS, $P = 0.13$.

A FODMAP-restricted diet was shown to be more effective than dietary guidelines in IBS

FODMAP

- Most patients found to be sensitive to FODMAPs often observe symptom improvement within the first week of trying the FODMAP-restricted diet.
- There is a clear increase in efficacy over the first 6 weeks.
- It is recommended that patients who may benefit from the diet attempt strict adherence for at least 6–8 weeks

Probiotics

Caveats in the assessment of probiotics on IBS

- IBS- heterogenic population
- IBS- problematic assessment tools
- “Probiotics”: not all alike
- Prescribing a patient “probiotics” is almost like prescribing a patient “antibiotics”
- Strain selection, dose and viability may be crucial for efficacy

Reference	*n*	Intervention and daily dose	Duration (weeks)	Result
Kajander *et al.*[65]	103	*L. GG, L. rhamnosus LC705, B. breve Bb99, Propionibacterium freudenreichii* spp *shermanii* JS	26	Significant reduction in GSS ($P<0{\cdot}015$)
Kim *et al.*[54]	48	VSL#3; 10^{11}	4	Failed to show improvement in bloating scores (PEP; $P<0{\cdot}19$) Reduction in flatulence scores ($P<0{\cdot}01$)
Bausserman *et al.*[53].	50	*L. GG*; 10^{10}	6	PEP defined as resolution of pain; failed to show benefit treatment arm *v.* placebo (40% *v.* 44%; $P<0{\cdot}77$; children)
Niv *et al.*[56]	54	*L. reuteri* ATCC 55730; 10^{8}	26	Failed to show benefit in GSS over placebo
O'Mahony *et al.*[37]	77			t in *us* failed to
Tsuchiya *et al.*[80]	68			)
Kim *et al.*[78]	25*			in bloating
Sen *et al.*[57]	12			ebo
Niedzielin *et al.*[55]	40			*v.* 55%
Nobaek *et al.*[62]	60			
Enck *et al.*[59]	298			·001)
Williams *et al.*[79]	52			ebo
Andriulli *et al.*[58]	267			in GSS
Drouault-Holowacz *et al.*[69]	100			in GSS
		and *S. thermophilus* LA 104 (13%); 10^{10}		
Sinn *et al.*[67]	40	*L. acidophilus* SDC 2012, 2013; 10^{9}	4	Significant reduction in abdominal pain ($P=0{\cdot}011$)
Kajander *et al.*[60]	86	*L. GG, L. rhamnosus LC705, B. breve Bb99, Propionibacterium freudenreichii* spp *shermanii* JS	20	Significant reduction in GSS ($P<0{\cdot}008$)
Guyonnet *et al.*[70]	274†	*B. animalis* DN 173 010	6	Although significant improvement over baseline, no benefit over placebo
Whorwell *et al.*[61]	362	*B. infantis 35624*; 10^{8}	4	Reduction in pain score (PEP; $P<0{\cdot}03$) Reduction in GSS ($P<0{\cdot}01$)
Gawronska *et al.*[63]	37‡	*L. GG*; 10^{9}	4	PEP defined as resolution of pain; 33% *v.* 5·1% ($P<0{\cdot}04$; children)

- Different bacteria
- Different dosing
- Mixed probiotics
- Different end points

Parkes GS Proceedings of the Nutrition Society (2010), 69, 187–194

The greatest efficacy data in treating IBS are:

- B. infantis 35624 (women : diarrhea predominant)
- E. coli DSM 17252
- Both these probiotics have had initial successful trials supported by larger multi-centre studies

Parkes GS Proceedings of the Nutrition Society (2010), 69, 187–194

Antibiotic Treatment of D-IBS

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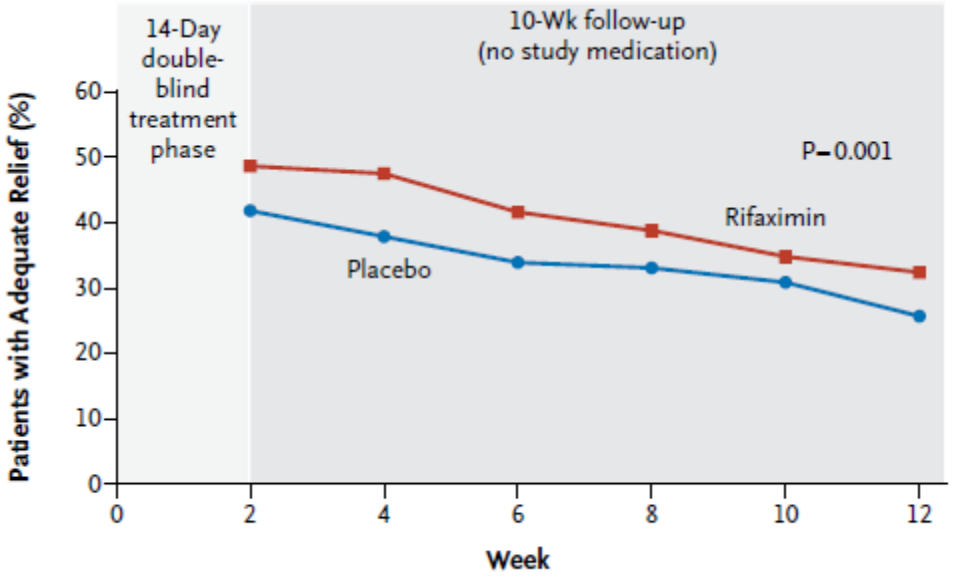
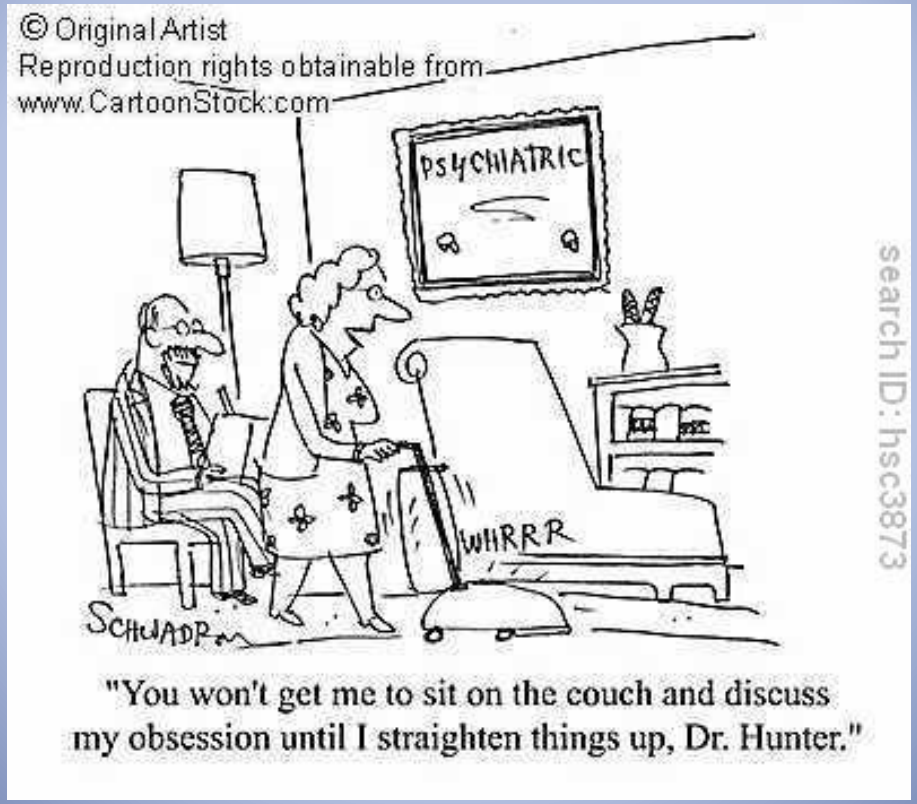


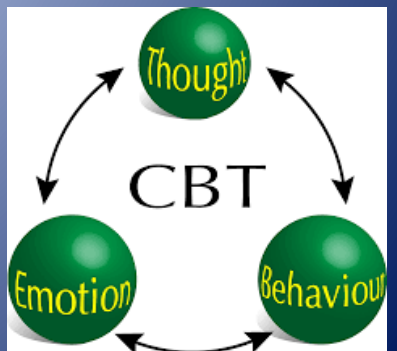
Behavioral therapies



Behavioral Therapies

- CBT has a direct effect on global IBS symptom improvement, independent of its effects on psychological distress.

- Symptom benefit with CBT may be mediated through changes in neural activity of cortical-limbic regions that subserve hypervigilance and emotion regulation.



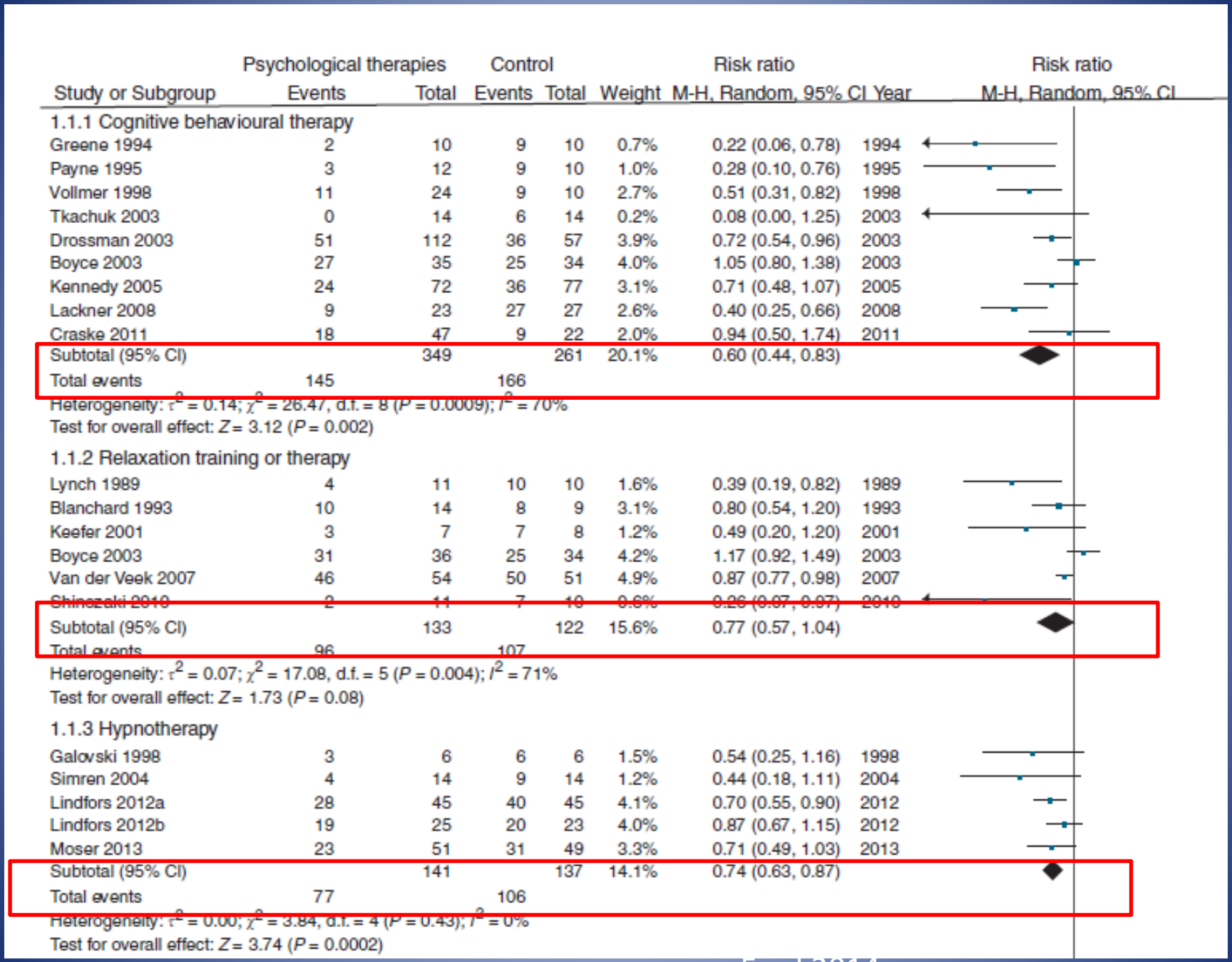
Relaxation Training

- Relaxation techniques are to train patients to counteract physiologic squeal of stress or anxiety.
- Five studies have assessed efficacy of relaxation therapy in IBS.
- Relaxation alone or in combination with CBT and other therapies can be beneficial for IBS symptoms.

Hypnotherapy

- Hypnotherapy has been shown to be effective for the treatment of IBS with a favorable impact on refractory IBS symptoms.

- The mechanism is unclear, although there is some evidence that it reduces gut contractility and normalizes pain thresholds after balloon rectal distension.


Psychological therapies
Control
Risk ratio
Risk ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
1.1.1 Cognitive behavioural therapy
Greene 1994 2 10 9 10 0.7% 0.22 (0.06, 0.78) 1994
Payne 1995 3 12 9 10 1.0% 0.28 (0.10, 0.76) 1995
Vollmer 1998 11 24 9 10 2.7% 0.51 (0.31, 0.82) 1998
Tkachuk 2003 0 14 6 14 0.2% 0.08 (0.00, 1.25) 2003
Drossman 2003 51 112 36 57 3.9% 0.72 (0.54, 0.96) 2003
Boyce 2003 27 35 25 34 4.0% 1.05 (0.80, 1.38) 2003
Kennedy 2005 24 72 36 77 3.1% 0.71 (0.48, 1.07) 2005
Lackner 2008 9 23 27 27 2.6% 0.40 (0.25, 0.66) 2008
Craske 2011 18 47 9 22 2.0% 0.94 (0.50, 1.74) 2011
Subtotal (95% CI) 349 261 20.1% 0.60 (0.44, 0.83)
Total events 145 166
Heterogeneity: $\tau^2 = 0.14$; $\chi^2 = 26.47$, d.f. = 8 ($P = 0.0009$); $I^2 = 70\%$
Test for overall effect: $Z = 3.12$ ($P = 0.002$)
1.1.2 Relaxation training or therapy
Lynch 1989 4 11 10 10 1.6% 0.39 (0.19, 0.82) 1989
Blanchard 1993 10 14 8 9 3.1% 0.80 (0.54, 1.20) 1993
Keefer 2001 3 7 7 8 1.2% 0.49 (0.20, 1.20) 2001
Boyce 2003 31 36 25 34 4.2% 1.17 (0.92, 1.49) 2003
Van der Veek 2007 46 54 50 51 4.9% 0.87 (0.77, 0.98) 2007
Shinozaki 2010 2 11 7 10 0.6% 0.26 (0.07, 0.97) 2010
Subtotal (95% CI) 133 122 15.6% 0.77 (0.57, 1.04)
Total events 96 107
Heterogeneity: $\tau^2 = 0.07$; $\chi^2 = 17.08$, d.f. = 5 ($P = 0.004$); $I^2 = 71\%$
Test for overall effect: $Z = 1.73$ ($P = 0.08$)
1.1.3 Hypnotherapy
Galovski 1998 3 6 6 6 1.5% 0.54 (0.25, 1.16) 1998
Simren 2004 4 14 9 14 1.2% 0.44 (0.18, 1.11) 2004
Lindfors 2012a 28 45 40 45 4.1% 0.70 (0.55, 0.90) 2012
Lindfors 2012b 19 25 20 23 4.0% 0.87 (0.67, 1.15) 2012
Moser 2013 23 51 31 49 3.3% 0.71 (0.49, 1.03) 2013
Subtotal (95% CI) 141 137 14.1% 0.74 (0.63, 0.87)
Total events 77 106
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.84$, d.f. = 4 ($P = 0.43$); $I^2 = 0\%$
Test for overall effect: $Z = 3.74$ ($P = 0.0002$)

Ford 2014

Drug Therapy

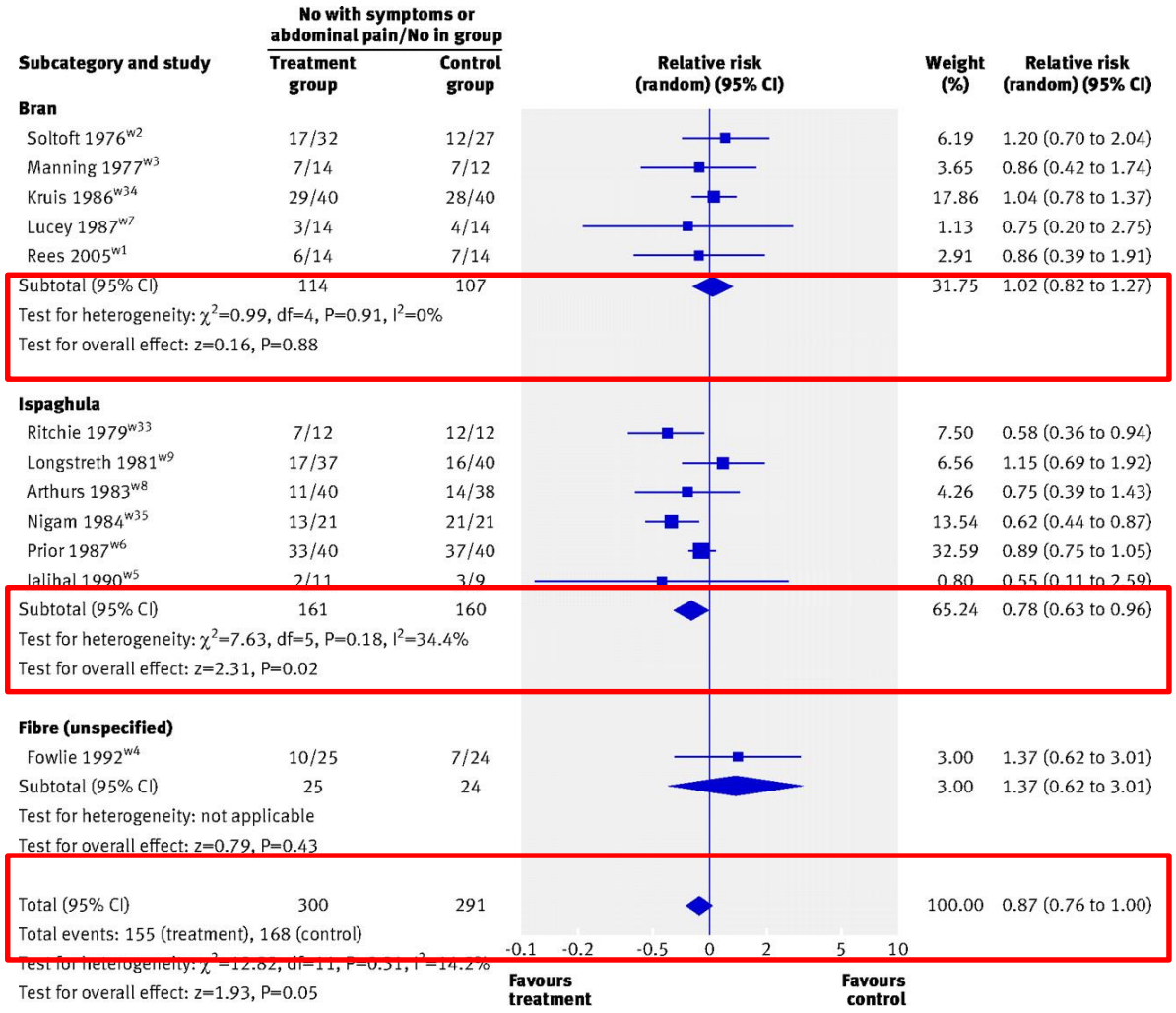
Peripherally Acting Therapies

- Most of these peripheral acting agents are primarily targeted at individual symptoms.
- The evidence supporting the use of these agents in IBS is largely anecdotal.

Fiber supplements

- The results of the 6 trials comparing psyllium and ispaghula with placebo were pooled, yielding a total of 321 patients with IBS, with 161 in the treatment arm.
- 52% of patients treated with psyllium had persistent IBS symptoms after treatment compared with 64% of those receiving placebo
- RR of symptoms not improving with psyllium was 0.78 compared with placebo with a NNT of 6.

Fig 2 Forest plot of randomised controlled trials of fibre versus placebo or low fibre diet in irritable bowel syndrome.



Alexander C Ford et al. BMJ 2008;337:bmj.a2313

Antispasmodics

- Abdominal pain or discomfort is a cardinal feature of IBS.
- Observation and clinical studies have suggested that an exaggerated motility response of the small bowel and colon to environmental stimuli may be responsible for the symptoms.
- For this reason antispasmodics have been and remain a mainstay of therapy for the symptoms of IBS.

Antispasmodics
ACG Task Force

- Certain antispasmodics (hyoscine, cimetropium, and pinaverium) may provide short-term relief of abdominal pain/discomfort in IBS .
- Evidence for long-term efficacy is not available.
- Evidence for safety and tolerability are limited.

Antispasmodics

- These agents are likely to be most effective in those patients with IBS with a predominant symptom of abdominal pain.

- These agents can worsen constipation and should therefore be used cautiously in patients with IBS with a predominance of constipation.

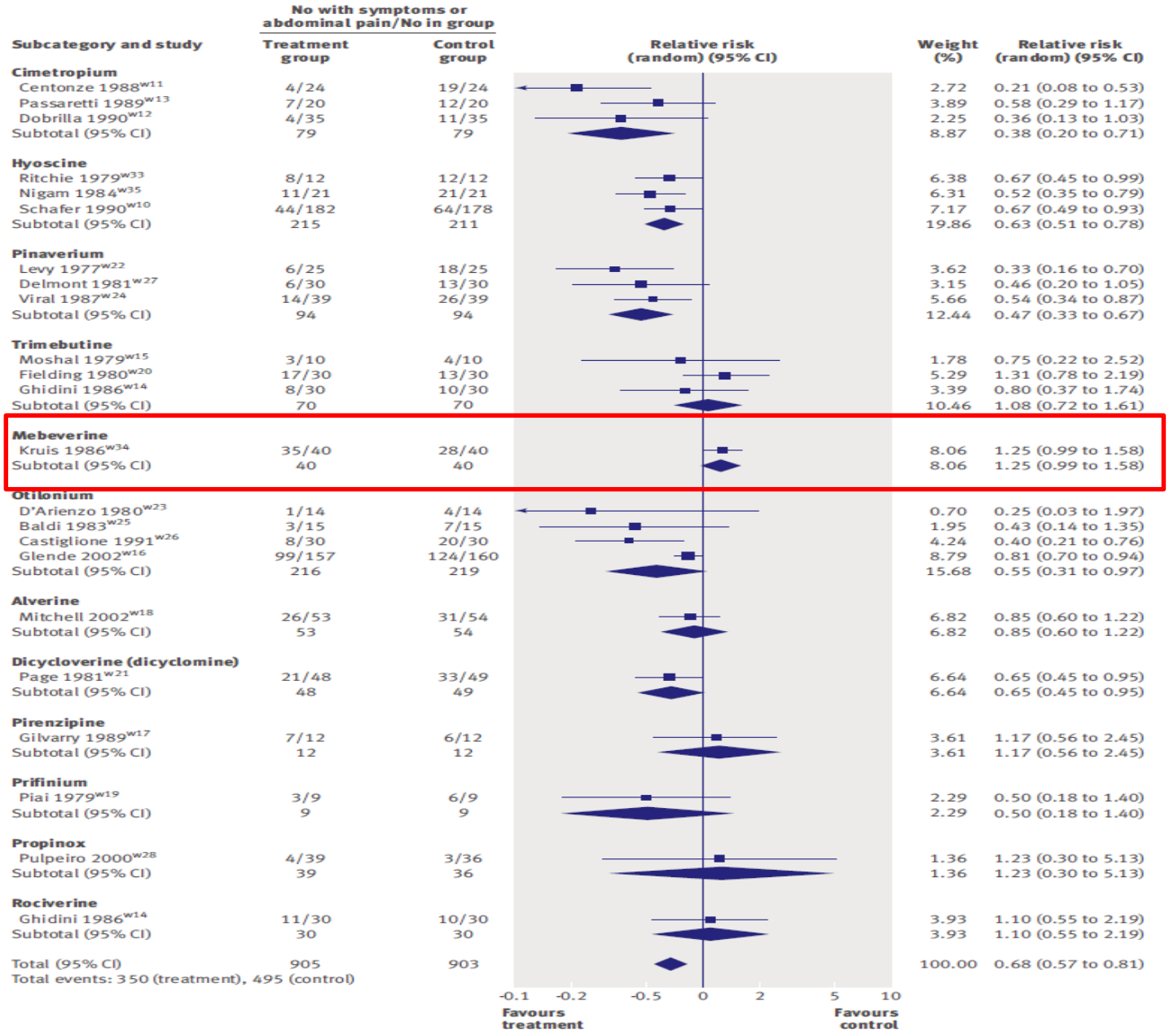


Fig 3 | Forest plot of randomised controlled trials of antispasmodics versus placebo in treatment of irritable bowel syndrome. Events are number of patients with either global symptoms of irritable bowel syndrome or abdominal pain unimproved or persistent after treatment. See bmj.com for individual tests for heterogeneity and for overall effect

Peppermint Oil

- Peppermint oil is effective and well tolerated in patients with IBS. (6 trails).

- It is commonly enteric coated or contains a barrier that controls the location in the digestive system where the oil is released.

Peppermint Oil

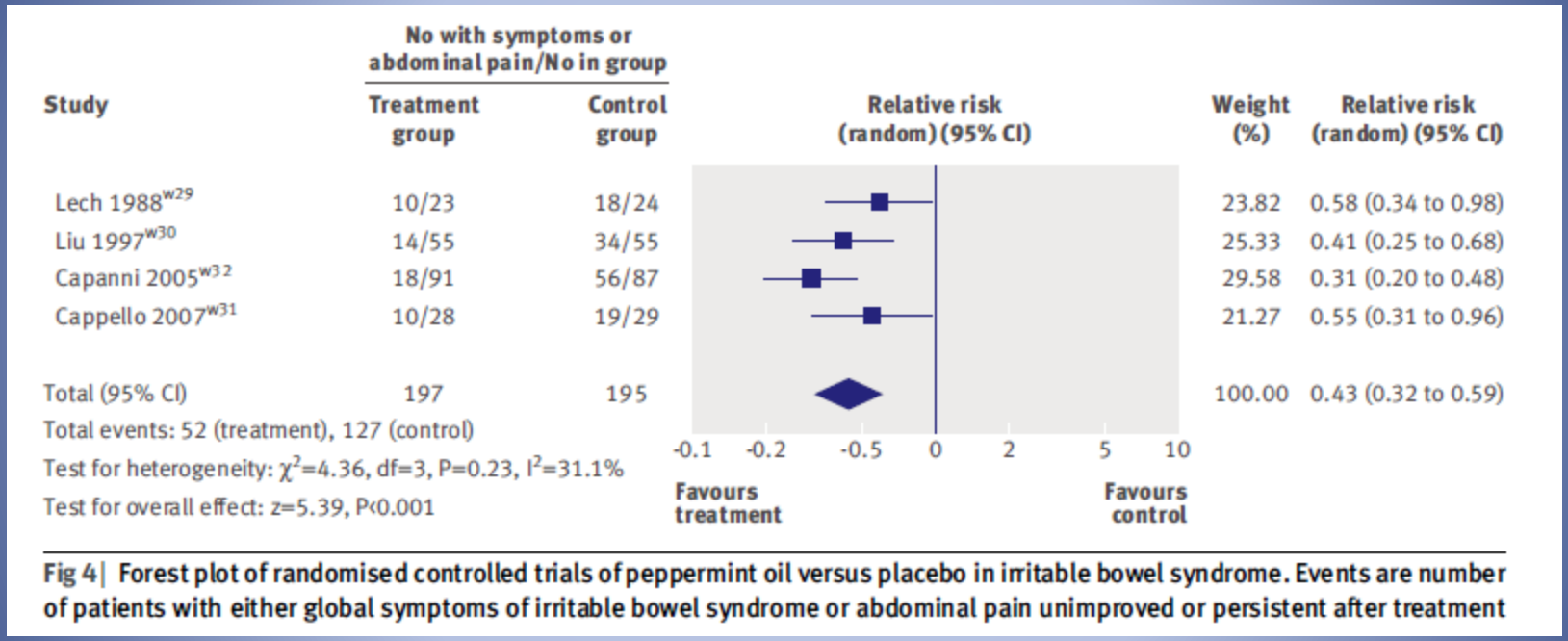
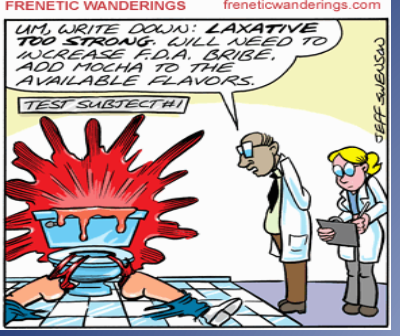


Fig 4| Forest plot of randomised controlled trials of peppermint oil versus placebo in irritable bowel syndrome. Events are number of patients with either global symptoms of irritable bowel syndrome or abdominal pain unimproved or persistent after treatment



Laxatives

- The use of laxatives in the treatment of IBS-C has evolved from their known effect on the symptoms of constipation.
- Only polyethylene glycol PEG has been assessed in the treatment of IBS.
- PEG was shown to improve stool frequency– but not abdominal pain.

Antidiarrheals

- Studies have reported accelerated small bowel and colon transit times as well as exaggerated motility patterns in those with IBS-D.

- Only loperamide has been evaluated in RCTs for the treatment of IBS.

Antidiarrheals

- Loperamide is an effective agent for treatment of diarrhea, improving stool frequency and stool consistency.
- Loperamide is not more effective than placebo at reducing abdominal pain or global symptoms of IBS.
- Safety and tolerability data on loperamide are lacking.

Serotonergic Agents

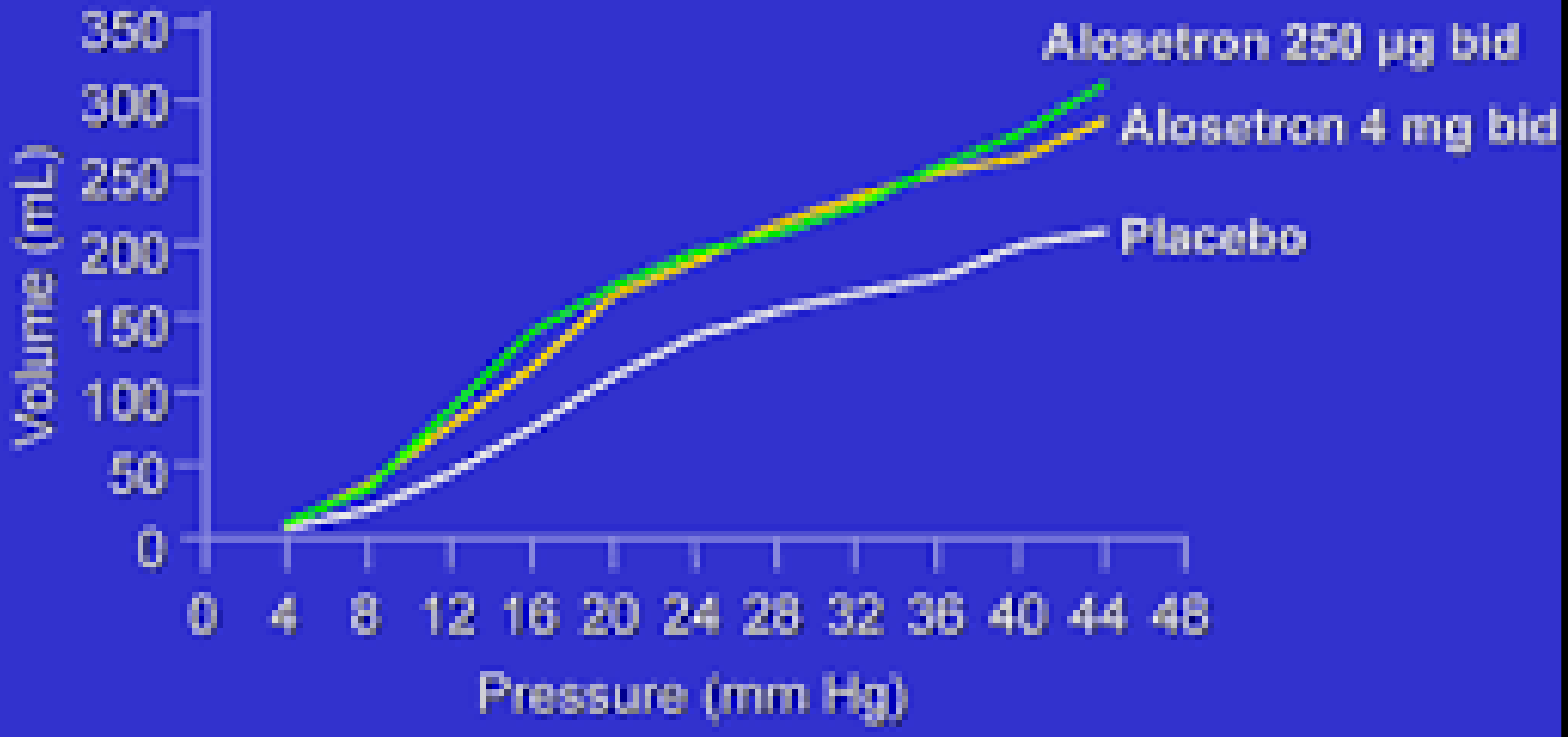
- Serotonin (5-HT) is the neurotransmitter primarily produced and stored in enterochromaffin cells located throughout the intestinal epithelium.
- 95% of total body concentration of 5-HT resides in the gastrointestinal tract.
- Acting through the intrinsic and extrinsic afferent nervous system of the GIT, 5-HT plays an important role in various aspects of gastrointestinal sensory, secretory, absorptive, and motility function.

Alosentron

- Alosetron is the only 5-HT_3 antagonist approved by FDA for the treatment of IBS-D
- Alosetron is more effective than placebo at relieving global IBS in male and female patients with IBS-D with diarrhea.
- Potentially serious side effects include constipation and colonic ischemia.
- The benefits and harms balance for alosetron is most favorable in women with IBS-D who have not responded to conventional therapies.

Not Available in Israel

Colonic Compliance



Delvaux M et al. Aliment Pharmacol Ther. 1998;12:849-855.

Chloride channel activator

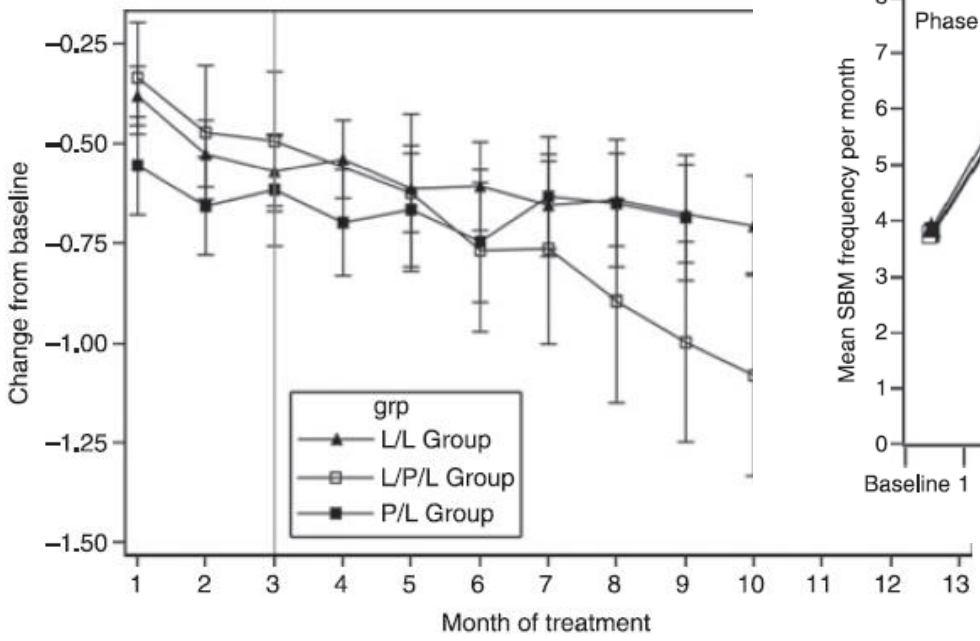
- Lubiprostone is the only chloride channel activator with FDA approval for the management of IBS-C.

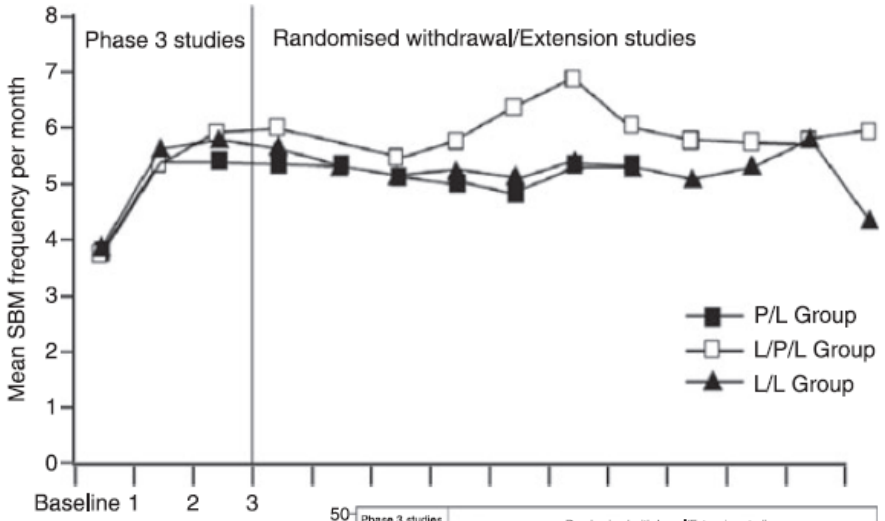
- Lubiprostone in a dose of 8µg twice daily is more effective than placebo in relieving global IBS symptoms in women with IBC-S

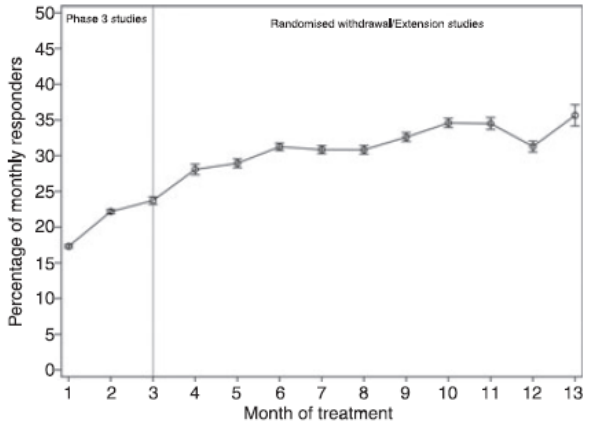
AP&T Alimentary Pharmacology and Therapeutics

Safety and patient outcomes with lubiprostone for up to 52 weeks in patients with irritable bowel syndrome with constipation

W. D. Chey*, D. A. Drossman†, J. F. Johanson‡, C. Scott§, R. M. Panas§ & R. Ueno§





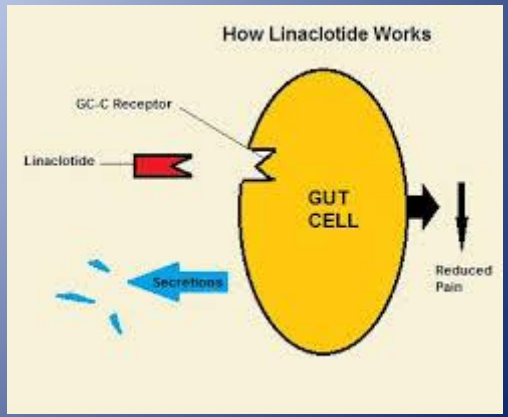


Chloride channel activator

Not Available in Israel

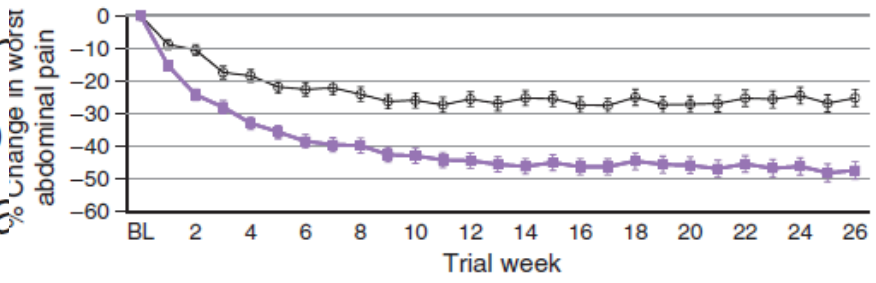
Guanylate Cyclase-C Agonist: Linaclotide

- Linaclotide increases intestinal fluid and electrolyte secretion, thereby improving the symptoms of IBS-C.
- Linaclotide also increases extracellular cGMP, which has been shown to reduce the mechanosensitivity of colonic nociceptors in animal models.

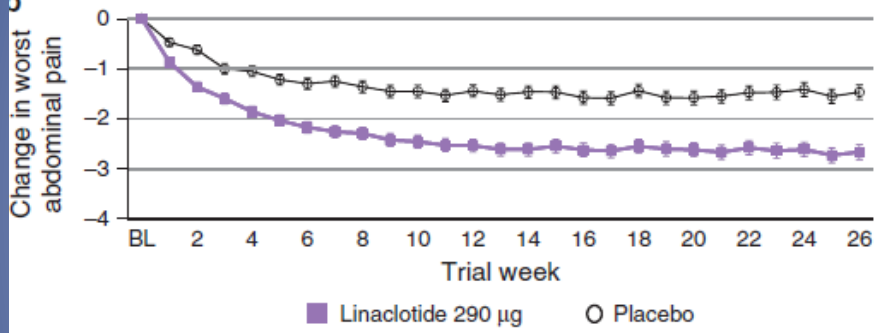


Lin… Co… Pla… …drome With …ized, Double-blind, …e Efficacy and Safety

William… Mark … Mollie … …Shiff, MD[4], Caroline B. Kurtz, PhD[3], …Shao, MS[3], Donald A. Fitch, MPH[3],



Least-squares mean percent change in worst abdominal pain ± standard error
$P < 0.001$ for each of the 26 weeks based on ANCOVA at each week



Least-squares mean change in worst abdominal pain ± standard error
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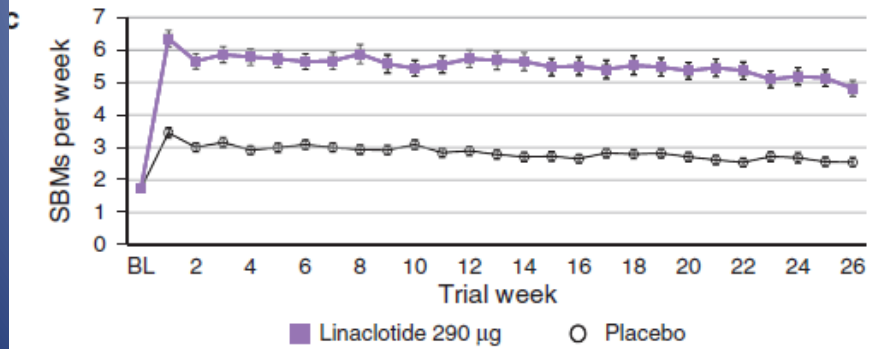
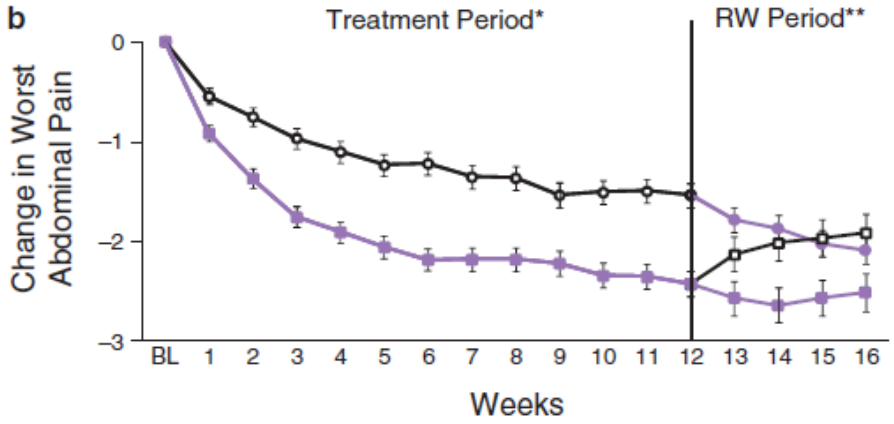


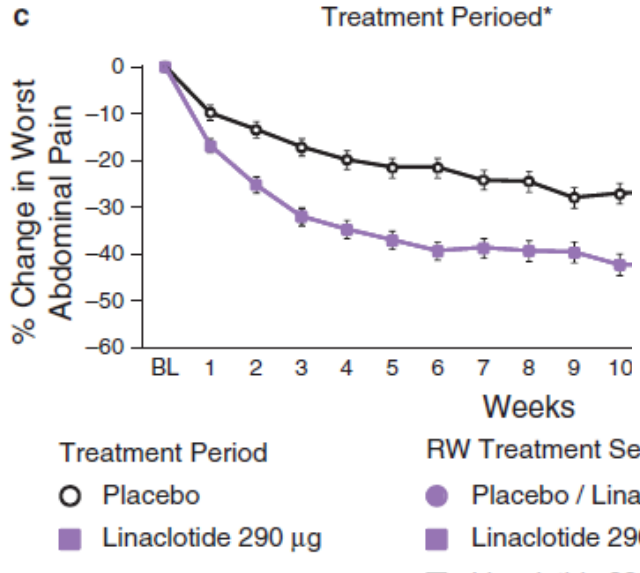
Mean SBMs per week ± standard error
$P < 0.0001$ for each of the 26 weeks based on ANCOVA at each week

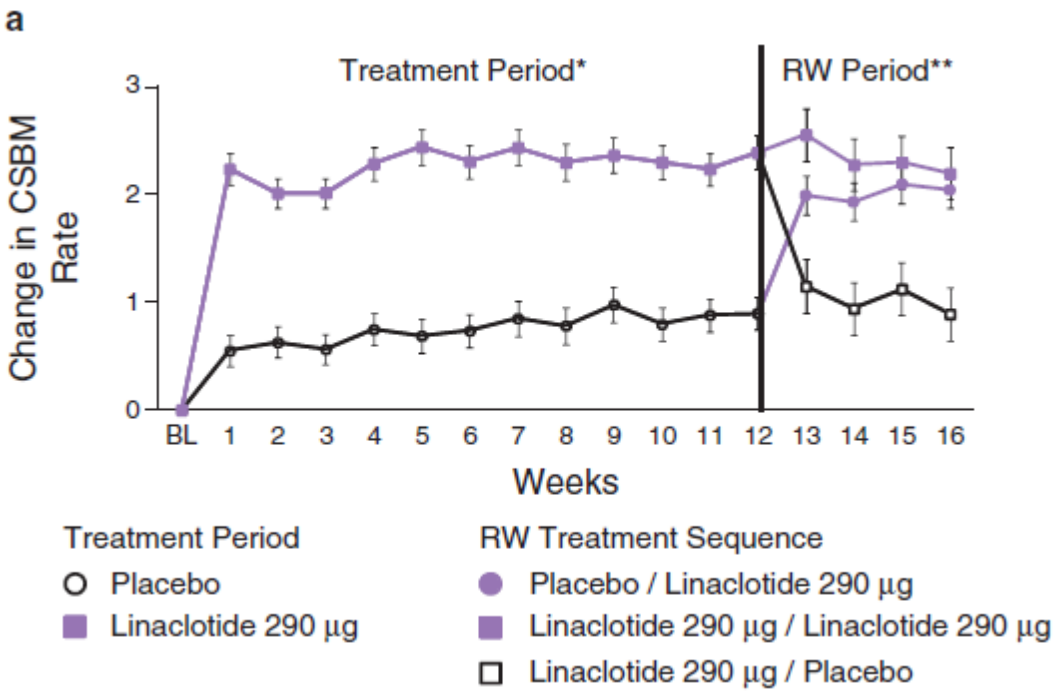
trolled Trial With a
val Period to Evaluate
aclotide in Irritable
ation

J. Lavins, MD[4], Mark G. Currie, PhD[4], Xinwei D. Jia, PhD



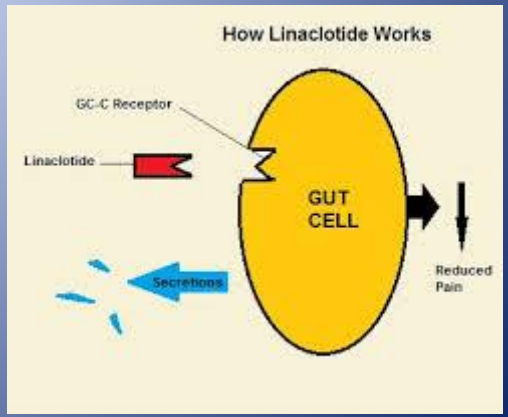
Least-squares mean change in worst abdominal pain ± stand
*$P<0.001$ for linaclotide patients compared to placebo patient
the 12 Treatment Period weeks (ANCOVA)
**$P<0.05$ for linaclotide-linaclotide patients compared to linac
patients for RW Period weeks 14, 15, and 16 (ANCOVA)





Guanylate Cyclase-C Agonist: Linaclotide

Not Available in Israel



Centrally Acting Therapies for Irritable Bowel Syndrome

- The use of psychotropic agents for FGIDs has grown significantly in the past 2 decades.
- Every 1 in 8 patients with IBS is offered an antidepressant.
- There is a decreased relative risk of persistent IBS symptoms with antidepressant treatment.
- NNT 3-4:1.

Centrally Acting Therapies

Potential benefits for use of psychopharmacological agents in FGIDs

Central effects:

1. Alters central pain perception: analgesia or antihyperalgesia.
2. Therapeutic effects on mood: to manage general anxiety, hypervigilance, symptom-related anxiety, agoraphobia, and increased stress responsiveness.
3. Treatment of associated psychiatric disorders: depression, posttraumatic stress disorder, somatization.
4. Treatment of associated sleep disturbances.

Peripheral effects:

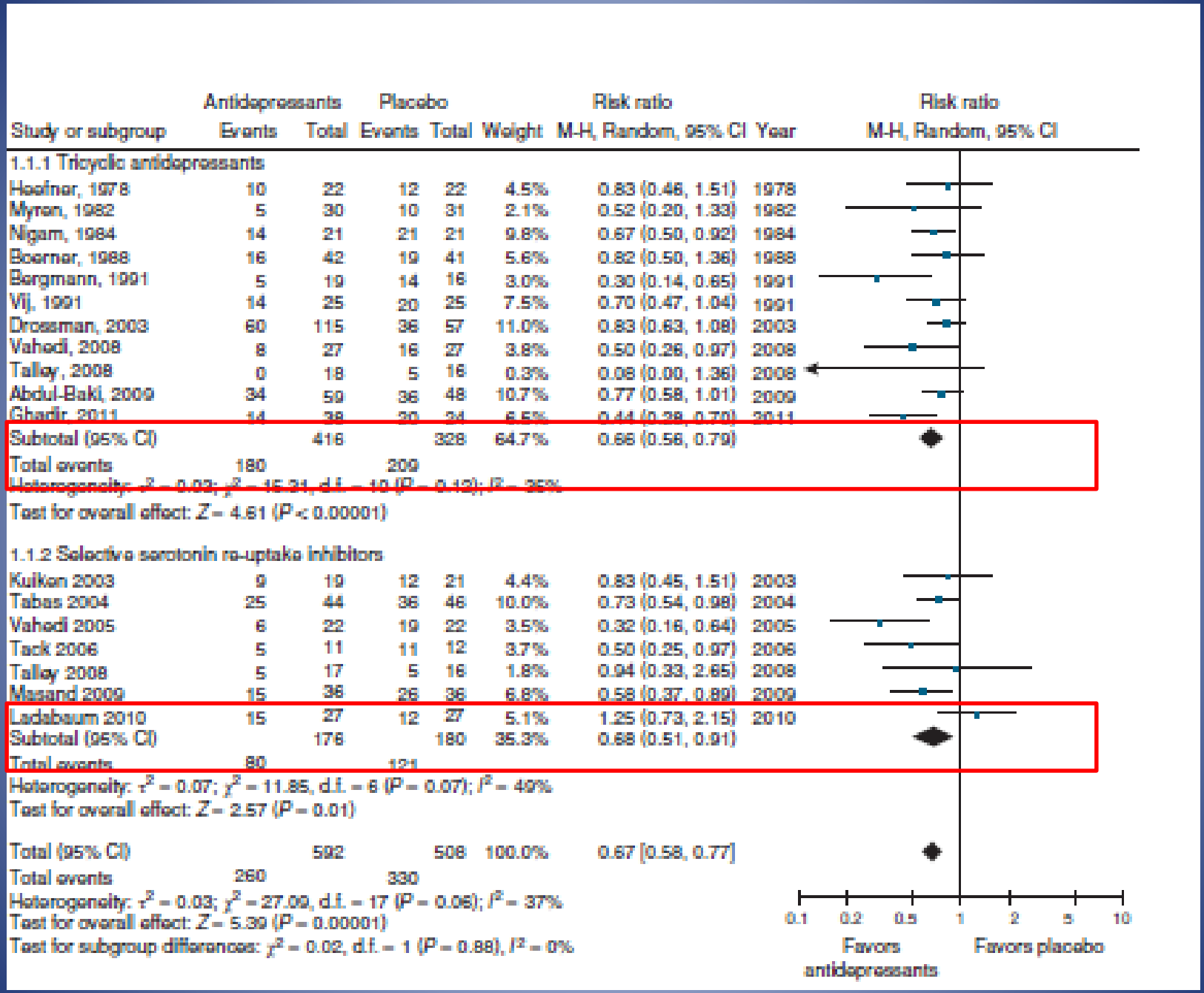
1. Peripheral analgesic effects: alters visceral afferent signaling.
2. Effect in GI physiology (motility and secretion) via effects on cholinergic, noradrenergic, and serotonergic pathways.
3. Smooth muscle effects on viscera, eg, gastric fundic relaxation.

Psychotropic agents

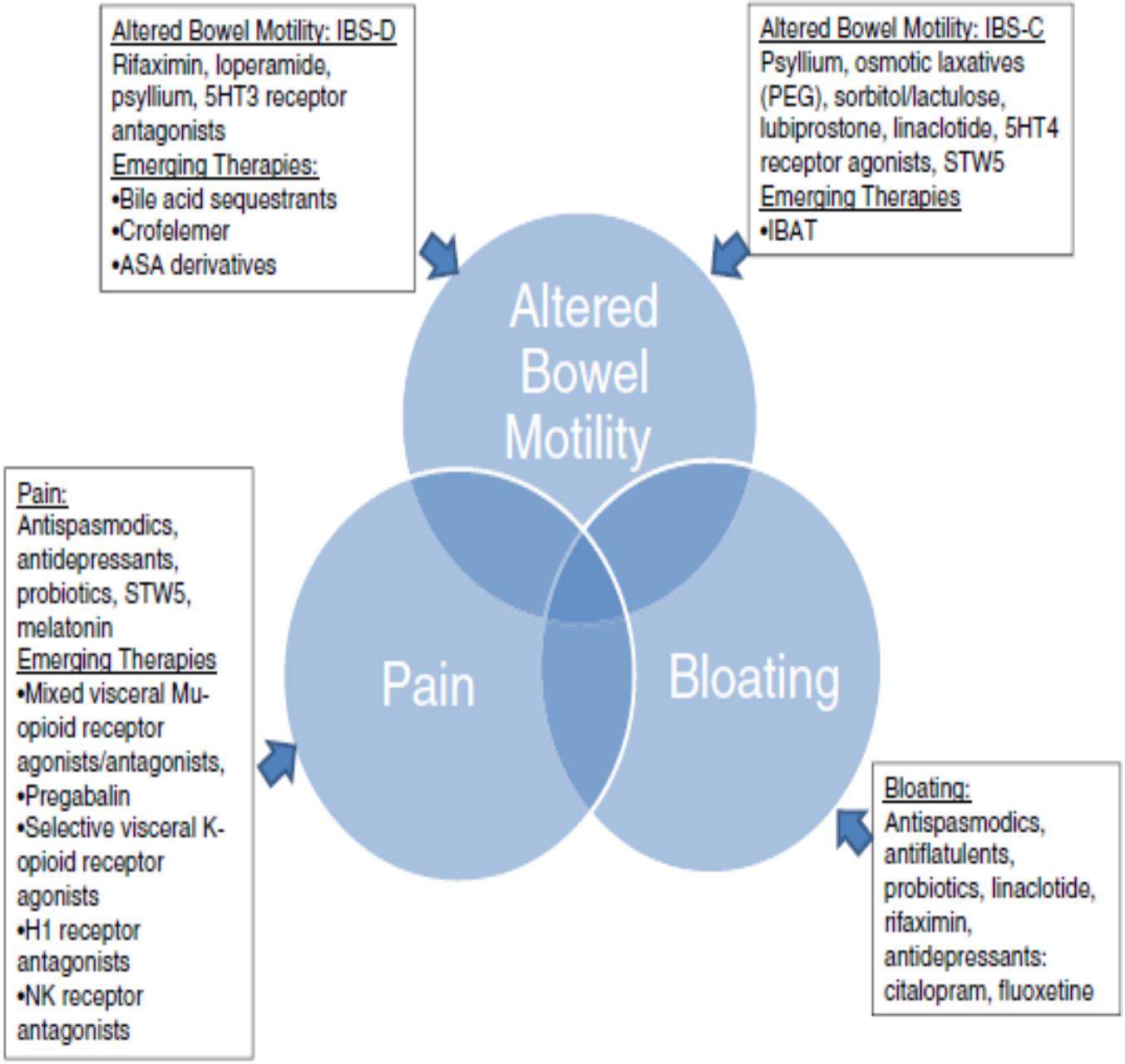
- Four major classes of psychotropic agents of interest in IBS are :

- ❑ **Tricyclic antidepressants**
- ❑ **Selective serotonin reuptake inhibitors**
- ❑ **Serotonin-norepinephrine reuptake inhibitors**
- ❑ **Atypical antipsychotics.**

- TCAs and SSRIs have been most widely studied.
- SNRIs are gaining popularity for treatment for other chronic pain conditions such as fibromyalgia and are likely to be further explored in IBS and other FGIDs.



Ford et al. 2014


Altered Bowel Motility: IBS-D
Rifaximin, loperamide, psyllium, 5HT3 receptor antagonists
Emerging Therapies:
•Bile acid sequestrants
•Crofelemer
•ASA derivatives
Altered Bowel Motility: IBS-C
Psyllium, osmotic laxatives (PEG), sorbitol/lactulose, lubiprostone, linaclotide, 5HT4 receptor agonists, STW5
Emerging Therapies
•IBAT
Altered Bowel Motility
Pain
Bloating
Pain:
Antispasmodics, antidepressants, probiotics, STW5, melatonin
Emerging Therapies
•Mixed visceral Mu-opioid receptor agonists/antagonists,
•Pregabalin
•Selective visceral K-opioid receptor agonists
•H1 receptor antagonists
•NK receptor antagonists
Bloating:
Antispasmodics, antiflatulents, probiotics, linaclotide, rifaximin, antidepressants: citalopram, fluoxetine

Complementary and Alternative Medicine

- CAMs are commonly used by patients with IBS, particularly acupuncture and herbal medicines.
- Well-controlled clinical trials are lacking to support CAM use in IBS.
- Nevertheless, several treatments, particularly some probiotics and herbs (eg, peppermint oil), suggest that they may have a benefit in IBS.

Prebiotics

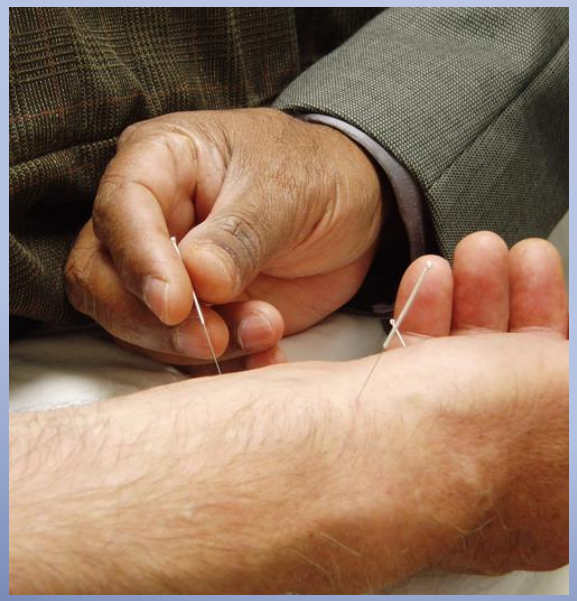
- Non-digestible food ingredient that act by selectively stimulating the growth and/or activity of one of a limited number of potentially health-promoting bacteria in the colon, most notably lactobacilli and bifidobacteria.
- Most commonly carbohydrates.
- Can also be found in a variety of food sources such as bananas, garlic, wheat, rye, and asparagus

Prebiotics

- Only a few studies have been conducted on the role of prebiotics in patients with IBS.
- The prebiotic trans-GOS improved IBS symptoms, which resulted in significant improvement in stool consistency, flatulence, and bloating.
- The prebiotic trans-GOS significantly increased fecal bifidobacteria counts.

Acupuncture

- Thought to alter visceral sensation and motility by stimulating the somatic nervous system and the vagus nerve.



Acupuncture

Table 1
Selected randomized controlled trials of acupuncture vs sham acupuncture for IBS

Study	Design	Patients	Control	Outcome Measures	Main Results
Forbes et al,[30] 2005	DB, parallel group 10 sessions over 10 wk	59 patients with Rome I IBS	Sham	Primary: decrease in symptom score at week 13 Others: weekly assessments	No difference between acupuncture and sham (40.7% vs 31.2%, *P*>.05) Both groups improved compared with baseline
Schneider et al	10 sessions over 5 wk	Study stopped early because of poor enrollment		by FDDQL Others: BDQ, PHQ-D, SF-36 at baseline, at the end of therapy, and at 3 mo	No difference between acupuncture and sham (11% and 10% increase in global FDDQL score) Both groups improved compared with baseline No significant AEs
Lembo et al,[19] 2009	DB, parallel group 6 session over 3 wk	230 patients with Rome II IBS	Sham	Primary: IBS-GIS Others: IBS-AR, IBS-SSS, IBS-QoL	No difference between acupuncture and sham (41% vs 32%, *P* = .25) Both groups improved compared with waiting-list group (37% vs 4%, *P*<.001) No significant AEs

No evidence of usefulness

Herbal Medicines

- Based on the use of plant and plant extracts as remedies to treat a variety of symptoms and diseases.
- Typically involves combining several herbs to obtain a desired effect.
- 4 studies were considered to be of good quality.
- These trials showed these herbal medicines to be effective in relieving IBS symptoms, including abdominal pain, constipation, and diarrhea.

Herbal Medicines

- The best studied herbal medicines for IBS are Tong xie yao fang (TXYF), STW 5 and STW 5-II.

- STW5 :
- bitter candytuft, chamomile flower, peppermint leaves, caraway fruit ,liquorice root, lemon balm leaves, celandine herbs, angelica root and milk thistle fruit

- STW5II :

bitter candytuft, chamomile flower, peppermint leaves, caraway fruit, liquorice root and lemonbalm leaves

Summary

Summary

- IBS is a significant medical problem
- IBS is multifactorial problem
- The available treatment optipns are restricted
- Integrative treatment approach is needed

NEVER,
under any circumstances,
take a sleeping pill and
a laxative on the same night.

reluctantmom