

Updates in Management of Irritable Bowel Syndrome

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Functional GI Disorders (FGIDs)

- Chronic recurrent digestive symptoms with no structural abnormalities
- Common FGIDs
 - Functional heartburn
 - Functional dysphagia
 - Functional chest pain
 - Functional dyspepsia (FD)
 - Belching disorder
 - Functional abdominal pain
 - Functional constipation
 - Irritable bowel syndrome (IBS)
 - Functional defaecation disorder

Rome IV Criteria for IBS

Recurrent abdominal *pain*, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria:

1. *Related to* defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool

Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Rome IV Criteria for IBS in Children

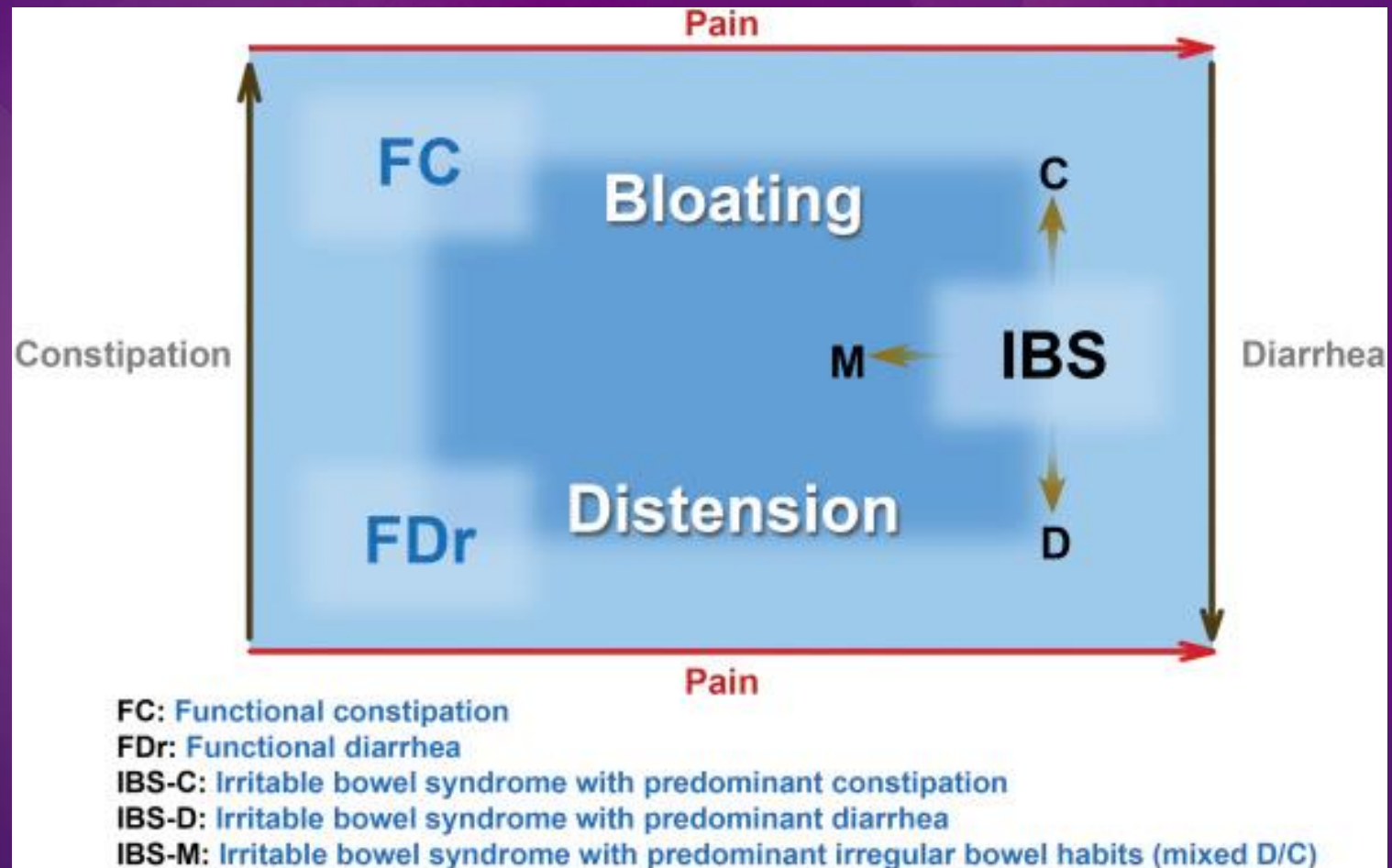
Abdominal **pain** at least 4 days per month associated with one or more of the following:

1. Related to defecation
2. A change in frequency of stool
3. A change in form (appearance) of stool

In children with constipation, the pain does not resolve with resolution of the constipation

Above criteria needs to be fulfilled for at least 2 months before diagnosis

IBS and Functional Bowel Disorders are spectrum disorders differentiated by pain



IBS Subtyping by Stool Consistency

Constipation

>25% Type 1 or 2: IBS-C
>25% Type 6 or 7: IBS-D
>25% in both: IBS-mixed
<25% in both: IBS-unclassified

Diarrhea

Bristol Stool Form Scale

Type 1



Separate hard lumps, like nuts (difficult to pass)

Type 2



Sausage-shaped but lumpy

Type 3



Like a sausage or snake but with cracks on its surface

Type 4



Like a sausage or snake, smooth and soft

Type 5



Soft blobs with clear-cut edges (passed easily)

Type 6



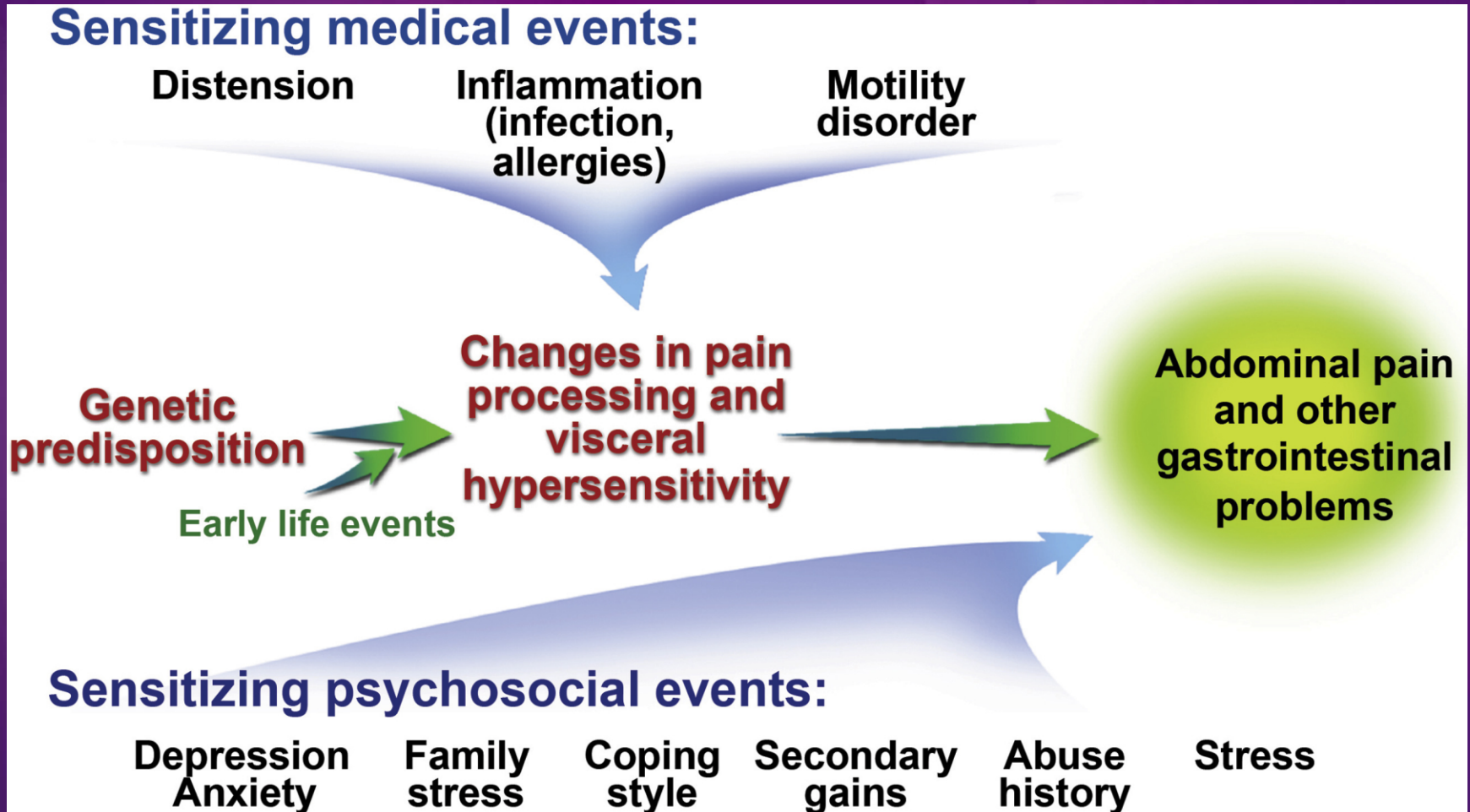
Fluffy pieces with ragged edges, a mushy stool

Type 7



Watery, no solid pieces (entirely liquid)

Pathophysiology of IBS in Children



Important differential diagnoses in Asia

- Inflammatory bowel disease
- Cancers: colorectal, ovarian, endometrial
- Enteric infection and small intestinal bacterial overgrowth
- Metabolic: Thyrotoxicosis, hypercalcemia, etc.
- Gynecological condition: endometriosis, fibroid, pelvic inflammatory disease
- Medications: NSAID, metformin, etc.
- Ischemic bowel disease
- Celiac disease
- Heavy metal poisoning

"Alarm features" in children

- Family history of inflammatory bowel disease, celiac disease or peptic ulcer disease
- Persistent right upper or lower abdominal pain
- Dysphagia and odynophagia
- Persistent vomiting
- Gastrointestinal blood loss
- Nocturnal diarrhea
- Peri-rectal disease
- Arthritis
- Unexplained fever
- Involuntary weight loss
- Deceleration of linear growth
- Delayed puberty

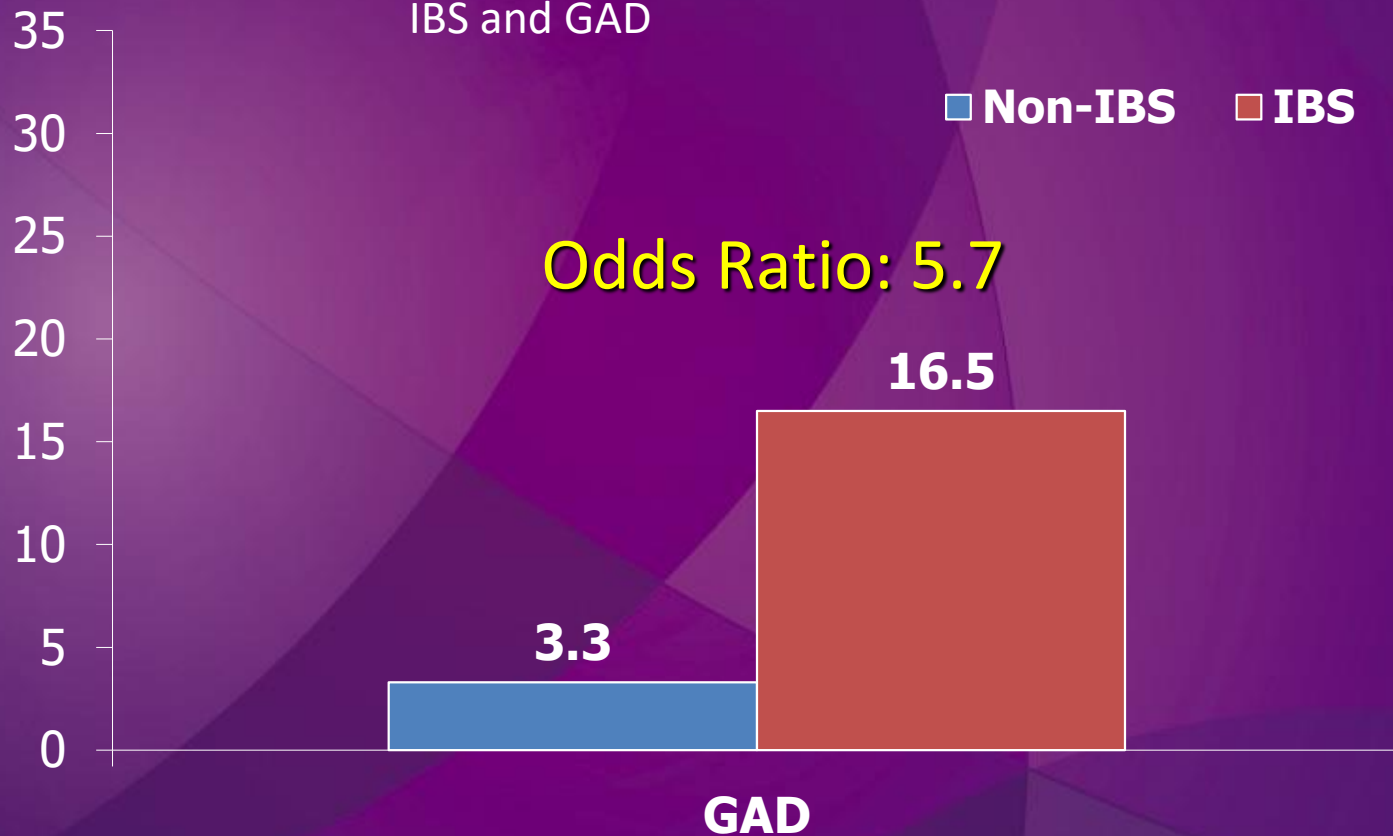
Irritable Bowel or Irritable Brain?



IBS is associated with Generalized Anxiety Disorder (GAD) in the community

Prevalence of GAD (%)

Community survey of 2005 subjects about symptoms of IBS and GAD

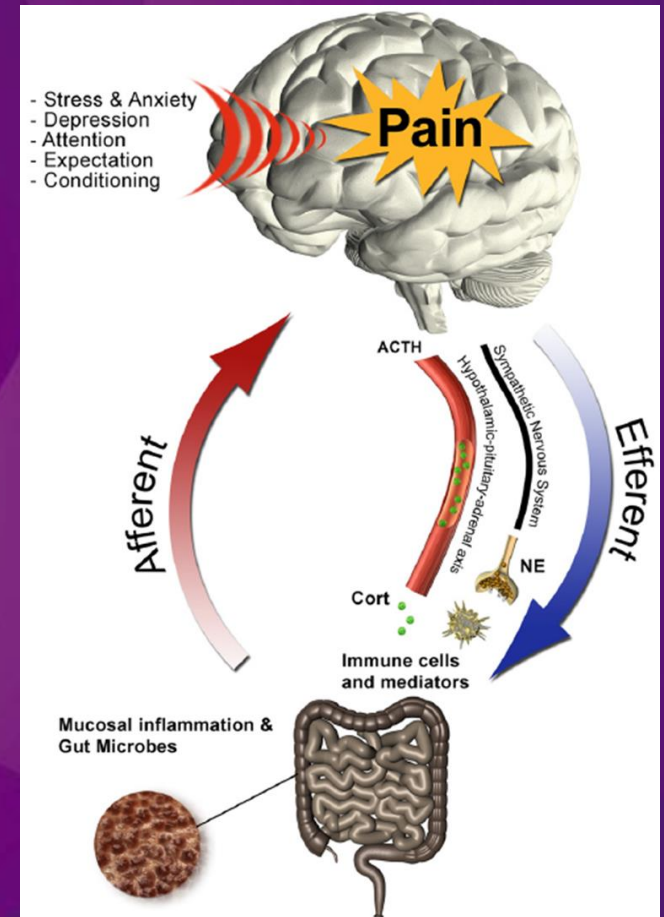


Prevalence of IBS: 5.4%

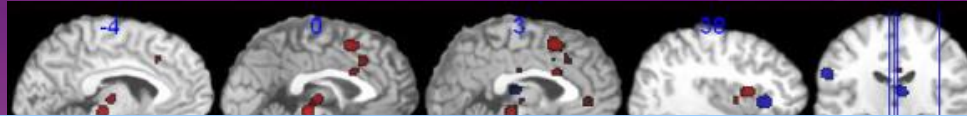
Prevalence of GAD: 4%

IBS: A Disorder of Gut-Brain Interaction (DGBI)

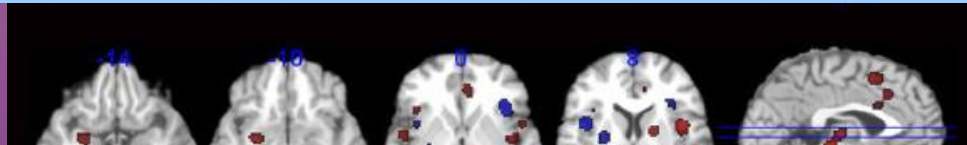
- Motility dysfunction
- Visceral hypersensitivity
- Psychiatric comorbidity
- Neuroendocrine dysfunction
- Genetics and epigenetics
- Immune activation
- Dysbiosis
- Diet



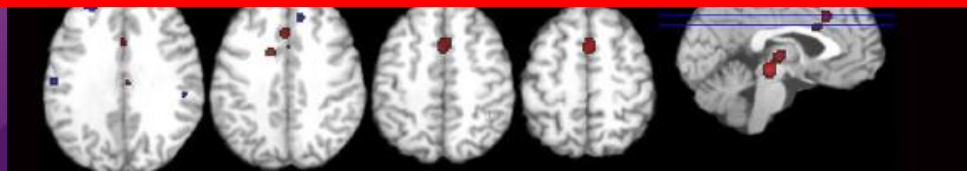
Aberrant emotional arousal and central pain modulation in IBS



IBS: pregenual anterior cingulate cortex, amygdala (**Emotional arousal**) and midbrain cluster (**Endogenous pain modulation**)



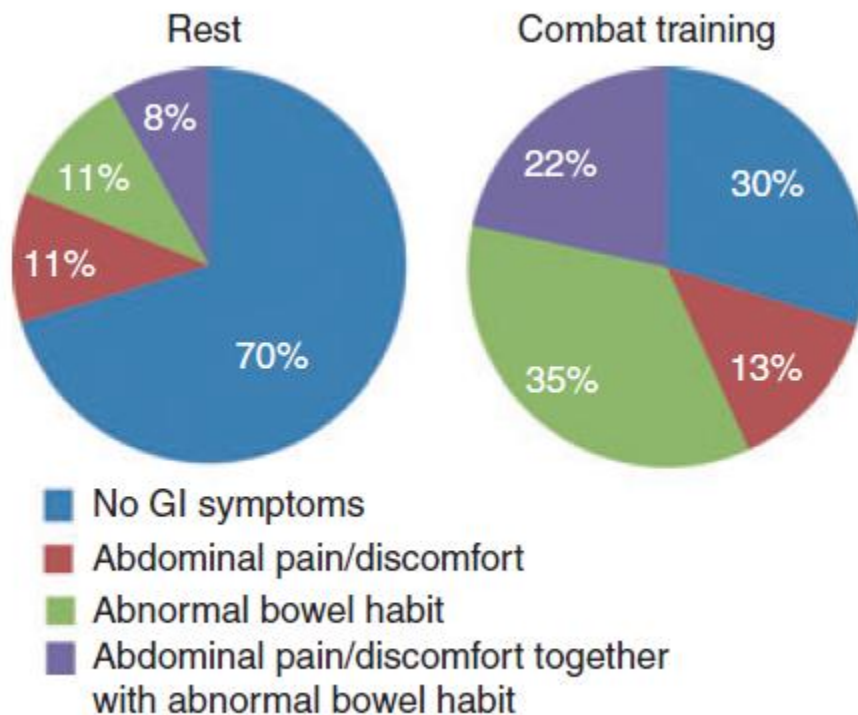
No difference in visceral afferent processing (ie, thalamus, insula, anterior mid-cingulate)



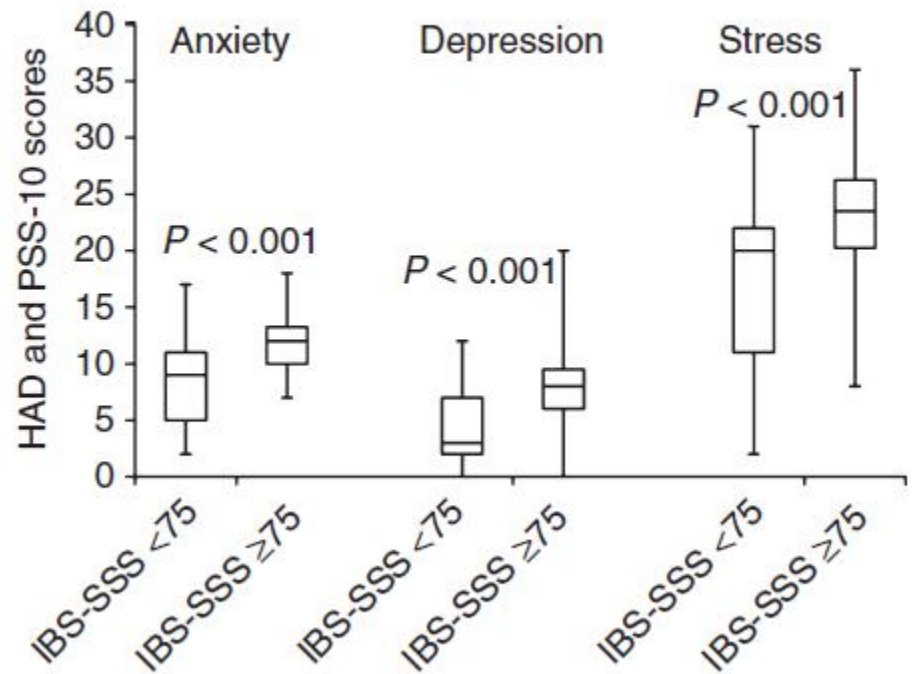
Quantitative meta-analysis of neuroimaging studies

Psychological stress is the primary event of both immune activation and GI symptoms

37 male soldiers underwent high-intensity combat training



HAD and PSS-10 scores in soldiers with IBS-SSS ≥ 75 or <75 during combat training



“Hints” for psychiatric comorbidity

- Sleep disturbance
- Fleeting somatic pain syndromes
- Chronological association between stress / major life event and symptoms
- Significant functional impairment
- Significant avoidance behavior
- Health anxiety
 - Repeated investigations
 - Relentless search for health information

Investigations

- Routine investigations are not recommended in patients aged <50 without alarm symptoms
- Blood tests: Complete blood counts, ESR, C-reactive protein, thyroid function, IgA tissue Transglutaminase (tTG)
- Stool tests: Culture, microscopy, C. difficile enterotoxin, faecal calprotectin
- Imaging: Colonoscopy, CT abdomen and pelvis

Management of IBS

- Therapeutic relationship
- Dietary advice
- Medical therapy
- Psychological intervention

IBS-associated Diet

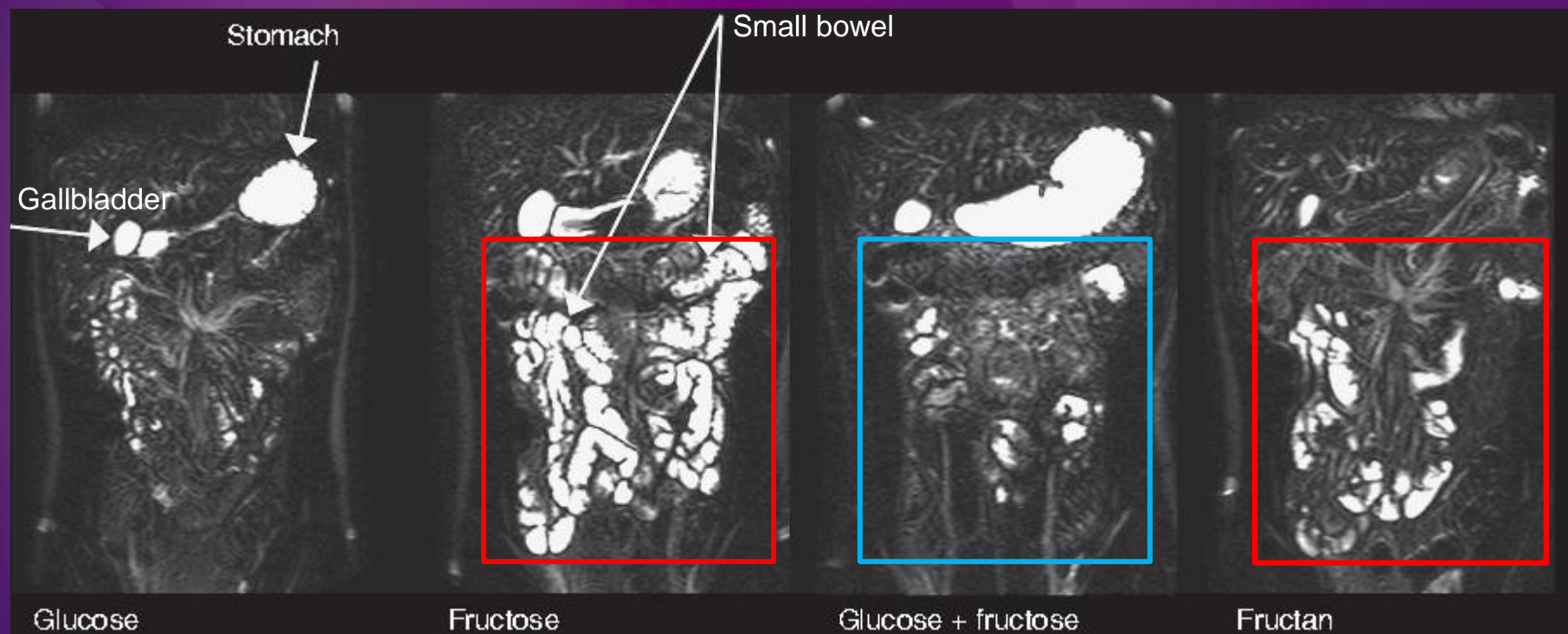


- FODMAP
- Sugar intolerance
- Fat
- Chili
- Gluten

Low FODMAP diet: Emerging 1st line treatment

- Fermentable Oligo-Di-Monosaccharides And Polyols
 - Fructose: Honey, watermelon
 - Lactose: Milk, ice-cream
 - Fructans: Wheat, garlic, onion
 - Galactans: Legumes, e.g. Beans, lentils, soybeans, cauliflower
 - Polyols: Sweeteners containing isomalt, mannitol, sorbitol, stone fruits (e.g. apples, apricots, cherries, peaches, plums)
- Low FODMAP diet improves IBS symptoms and quality of life
- ↓ Osmotic diarrhea, fermentation, altered gut microbiota, ↓ immune activation and visceral sensitivity
- ↓ Compliance to 50% in 8 weeks

“Sugar Intolerance” in IBS



MRI done 75 min after test drinks

Bulking agents and Antispasmodics

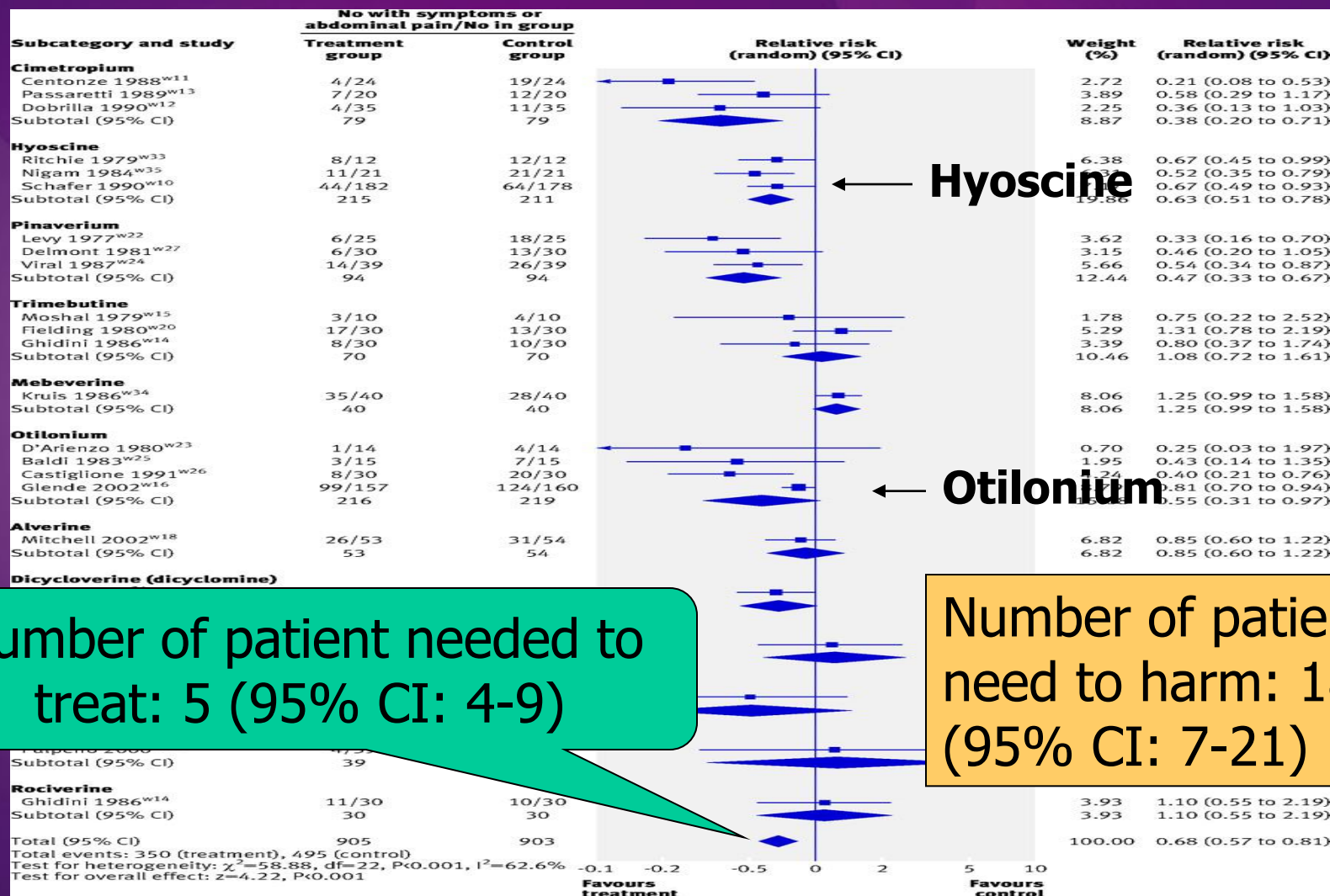
| | No. of studies | No. of patients | Relative risk (95% CI) of global improvement | P value |
|-----------------------|----------------|-----------------|--|-------------------|
| Bulking agents | 11 | 565 | 1.10 (0.91-1.33) | 0.32 |
| Antispasmodics | 22 | 1983 | 1.49 (1.25-1.77) | <0.0001 |

- Bulking agents or dietary fibre
 - Helps improve constipation
 - No benefit or may worsen abdominal pain
- Antispasmodics
 - NNT: 7 (pain), 5 (global improvement), 3 (symptom score)

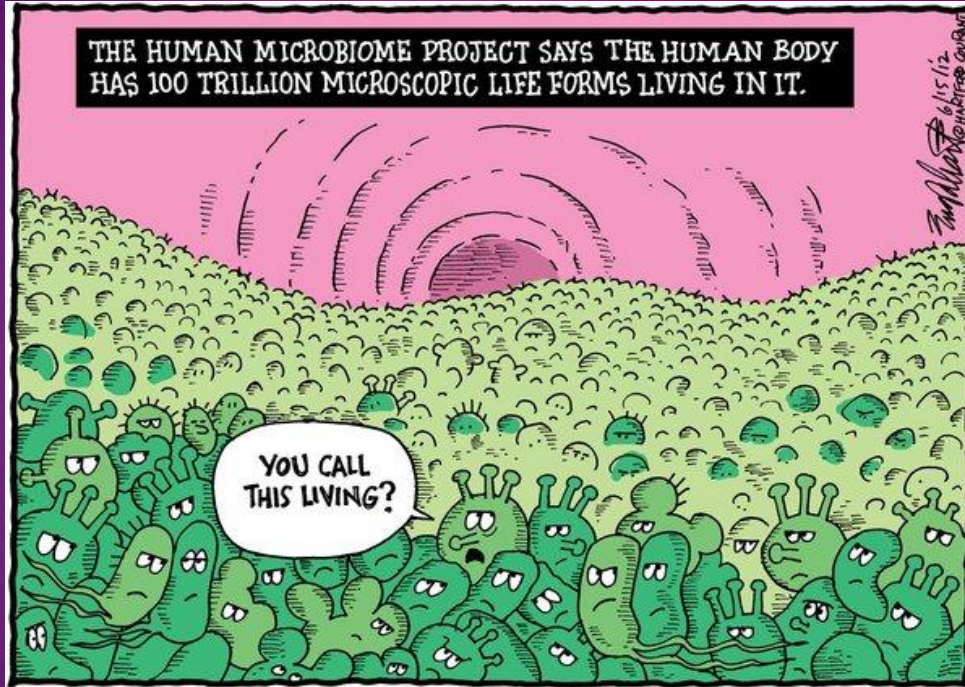
Antispasmodic remains the 1st line Medical Treatment

- Anticholinergic antispasmodics (e.g. Hyoscine)
- Non-anticholinergic antispasmodics (e.g. Otilonium, mebeverine)
- Peppermint oil

Efficacy Vs Side effects of Antispasmodics



How Dysbiosis leads to IBS?



- Fermentation
 - Immune activation
 - ↑ Intestinal permeability
 - Visceral hypersensitivity
 - Motility dysfunction
 - Malabsorption
 - Altered metabolome
 - Mood regulation
 - Epigenetic changes
-
- IBS-Diarrhea: ↓ Lactobacillus
 - IBS-Constipation: ↑ Methane-producing bacteria

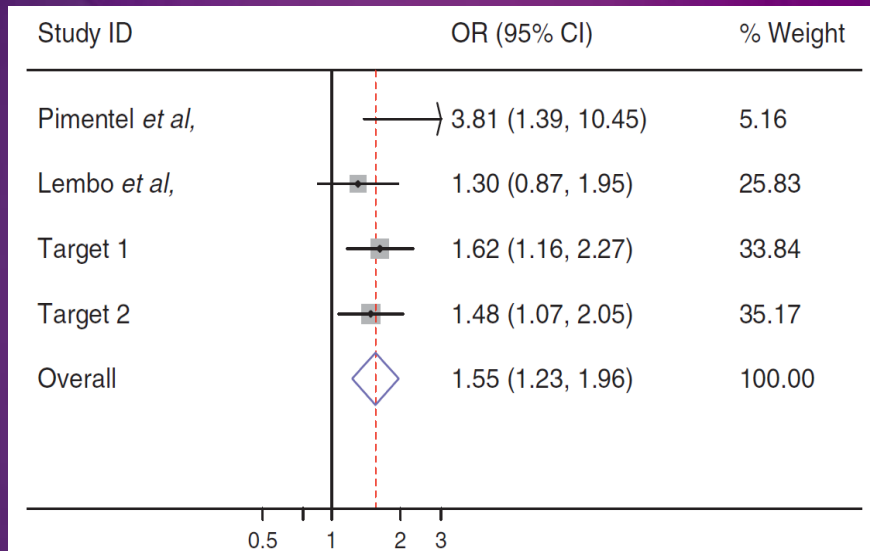
Probiotics: Positive results are consistent

| Probiotic | No. of studies | No. of subjects | Relative risk (95% C.I.) of persistent IBS symptoms |
|--------------------------|----------------|-----------------------------|---|
| Combination (e.g. VSL#3) | 12 | 609 (control: 588) | 0.81 (0.67-0.98) |
| Lactobacillus | 6 | 213 (control: 209) | 0.75 (0.54-1.04) |
| Bifidobacterium | 2 | 330 (control: 154) | 0.71 (0.44-1.16) |
| Escherichia | 2 | 208 (control: 210) | 0.86 (0.79-0.93) |
| Streptococcus | 1 | 32 (control: 22) | 0.72 (0.53-0.99) |
| ALL | 23 | 1392 (control: 1183) | 0.79 (0.70-0.89) |

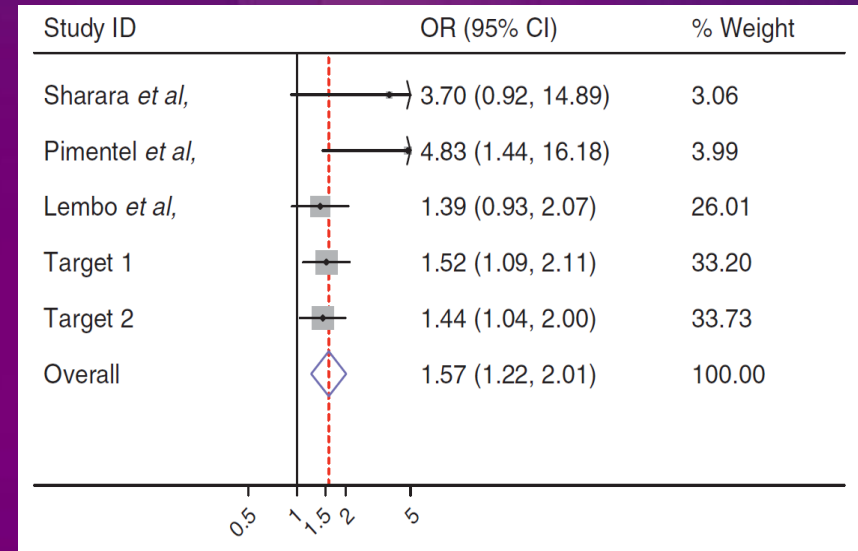
Unresolved: mechanism, best regimen, optimum delivery mode, durability of efficacy

Rifaximin reduces bloating in IBS

Poorly-absorbed, luminal-active antibiotic
5 Studies (N= 1,803)



Bloating: OR = 1.55 (95 % CI = 1.23 – 1.96); therapeutic gain = 9.9%
NNT = 10.1



Global improvement OR = 1.57 (95 % CI = 1.22 – 2.01); therapeutic gain = 9.8%
NNT = 10.2

Age strongly predictive of response (correlation coefficient of 0.97)

Antibiotics for IBS: Unresolved issues

Unclear mechanism

- Animal studies: ↓ mucosal inflammation and visceral hyperalgesia but microbiota data is lacking

Unclear long-term safety

- Good short-term safety profile: serious AEs (1.5% vs. 2.2%), discontinuation due to drug-related AEs (0.8% vs. 0.8%)
- Antibiotic resistance
- *Clostridium difficile* infection

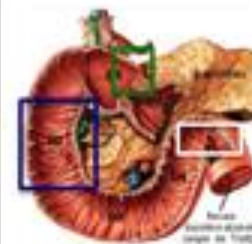
Unclear long-term efficacy

- Lack of long-term data or change in disease course

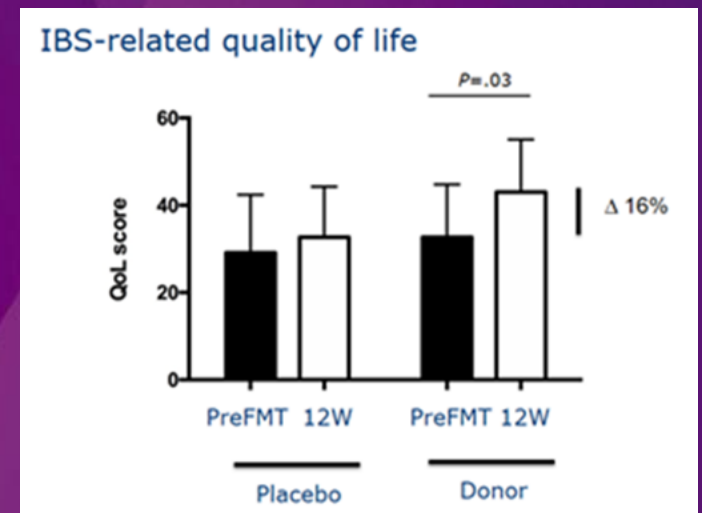
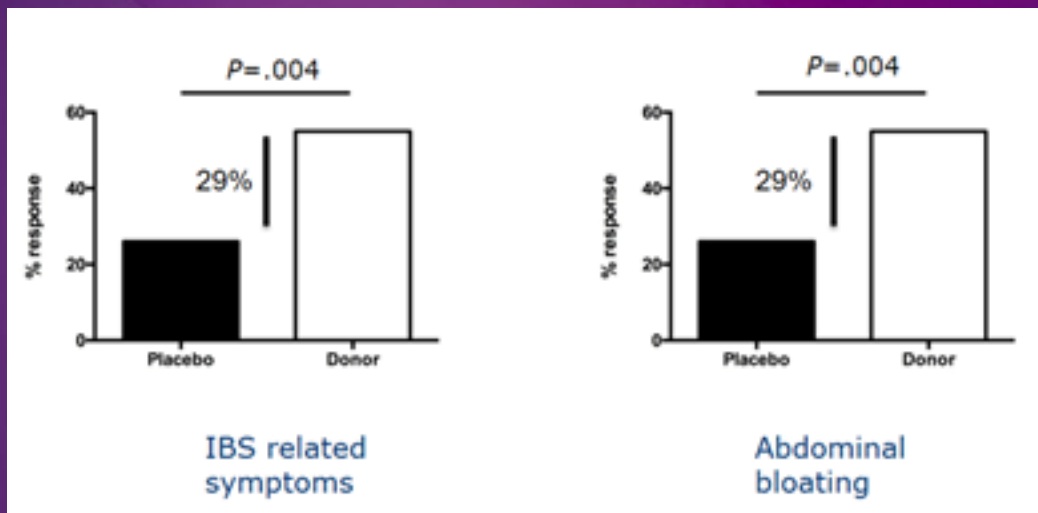
FMT for non-constipation IBS with bloating

62 patients with refractory IBS symptoms and predominant abdominal bloating (ROME III criteria), aged 18-75 years and without constipation were randomly assigned (2:1) to transplantation with fresh donor stool or with placebo

- FMT
 - Nasojejunal/duodenal administration
 - Cortrak™ probe
- 2 healthy donors
 - Rich microbial diversity
 - Proven efficacy in pilot trial
 - Screened repeatedly for infectious diseases
 - Fresh stools
- Placebo
 - Patients' own frozen stool



FMT reduces IBS symptoms and bloating



27% responders in remission at 1 year

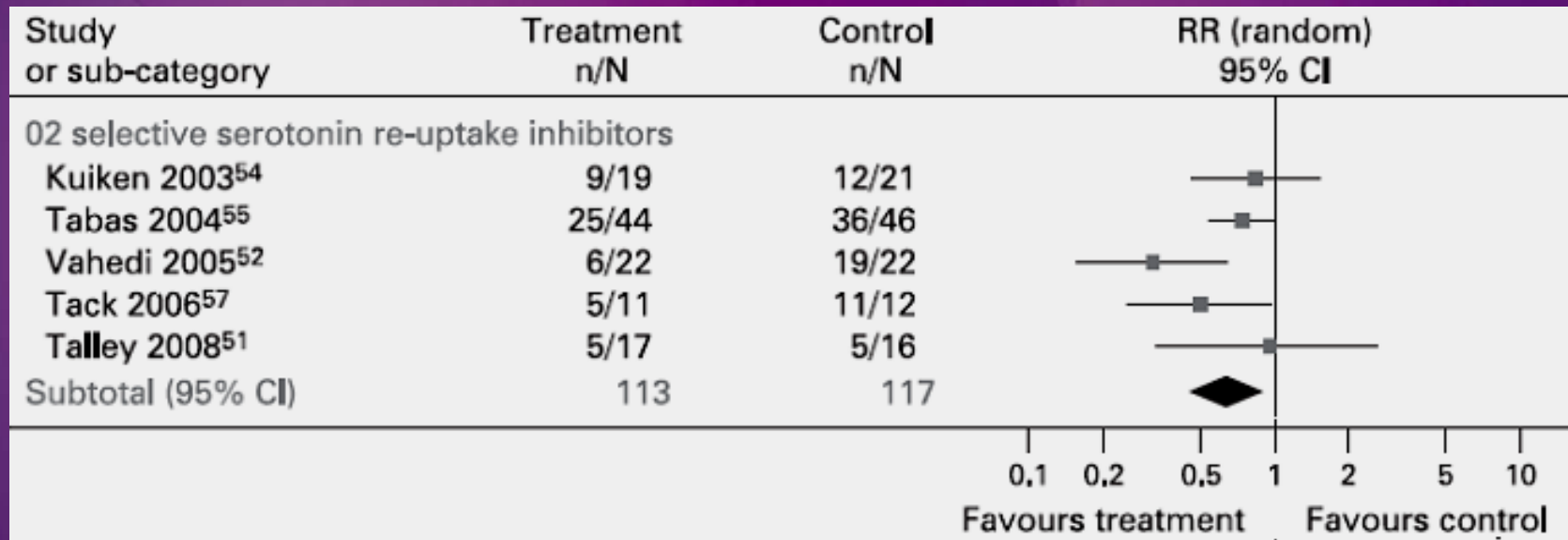
Serotonin (5-HT) receptor modulators

| Class | Drug | IBS subtypes with efficacy reported | Side effects |
|--|--------------|-------------------------------------|--|
| 5HT ₃ antagonist | Alosetron | IBS-D | Complicated constipation, ischemic colitis |
| | Cilansetron | IBS-D | |
| | Ramosetron | IBS-D | |
| 5HT ₄ agonist | Tegaserod | IBS-C, IBS-mixed | Myocardial infarction, stroke |
| | Prucalopride | Constipation | |
| 5HT ₄ agonist/ 5HT ₃ antagonist | Renzapride | IBS-C | Ischemic colitis |

Camilleri et al. Lancet 2000; Kellow et al. Gut 2003; Camilleri et al. N Engl J Med 2008
 Lembo et al. Aliment Pharmacol Ther 2010; Chey et al. Am J Gastroenterol 2008

Selective Serotonin Reuptake Inhibitor (SSRI) is the antidepressant of choice for IBS

Meta-analysis: 230 non-anxiety/depression IBS patients randomized to SSRI Vs placebo in 5 RCTs (Mostly from referral centers)



Relative risk of persistent IBS symptoms: 0.62 (95% CI, 0.45-0.87)

Number of patients needed to treat: 3.5 (95% CI: 2-14)

Secretagogue: Linaclotide (Guanylate cyclase C agonist) for IBS-C

839 IBS-C (Rome III) patients randomized to 12-week treatment with once-daily oral LIN 290 µg or placebo (PBO) (Phase 3 Trial)

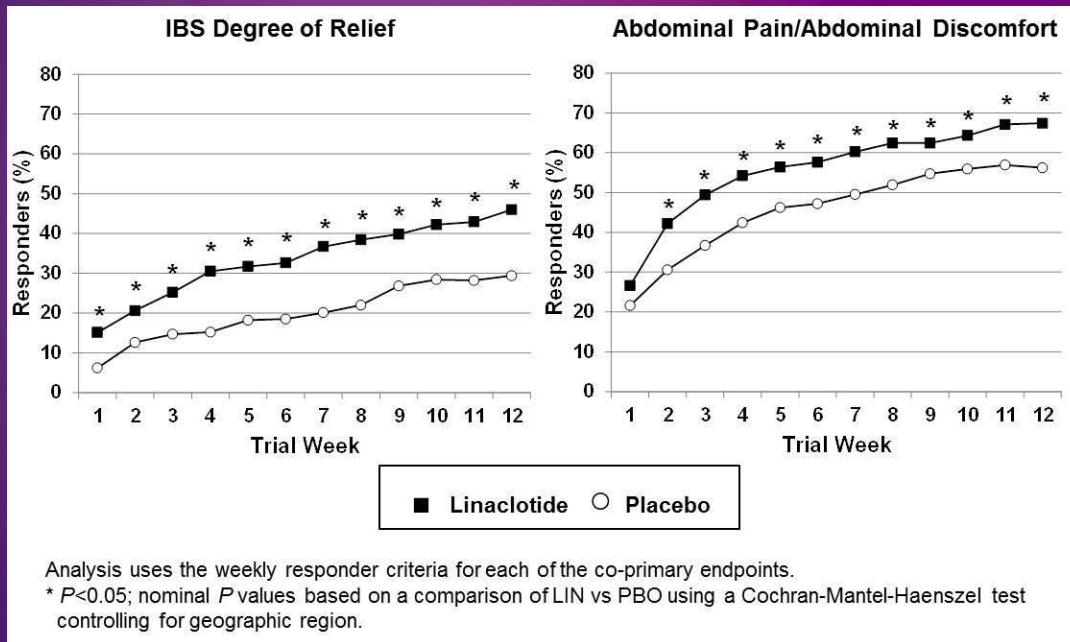
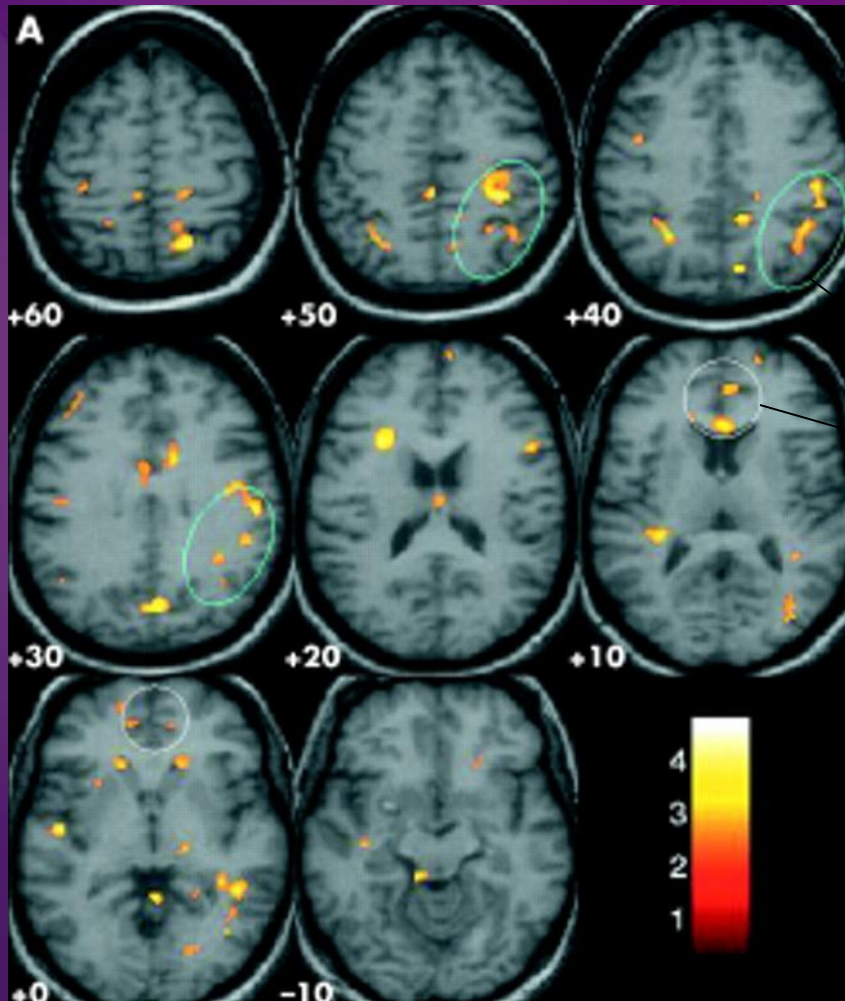


Table. Primary and Secondary Endpoint Results (ITT Population)

| | PBO (N=422) | LIN (N=417) | P value ^d |
|--|----------------|----------------|-------------------------|
| Co-primary Endpoints (% Responders)^a | | | |
| ≥30% decrease in abdominal pain or discomfort, with neither score worsening from baseline, for ≥6/12 weeks | 48.8 | 60.0 | 0.0010 |
| IBS degree of relief score ≤2 for ≥6/12 weeks ^b | 15.4 | 31.7 | <0.0001 |
| Secondary Endpoints (LS Mean Change from Baseline)^c | | | |
| CSBMs/week | 1.0 | 1.9 | <0.0001 |
| SBMs/week | 1.5 | 3.0 | <0.0001 |
| Stool consistency (7-point BSFS) | 0.8 | 1.5 | <0.0001 |
| Straining (5-point ordinal scale) | -0.7 | -1.0 | <0.0001 |
| Abdominal bloating (11-point NRS) | -0.9 | -1.5 | <0.0001 |
| Abdominal pain (11-point NRS) | -1.1 | -1.6 | <0.0001 |
| Abdominal discomfort (11-point NRS) | -1.0 | -1.5 | <0.0001 |

- Diarrhea reported in 9.4% of LIN patients Vs 1.2% of PBO patients.
- Low discontinuation rates due to diarrhea were low (0.7% LIN, 0.2% PBO).

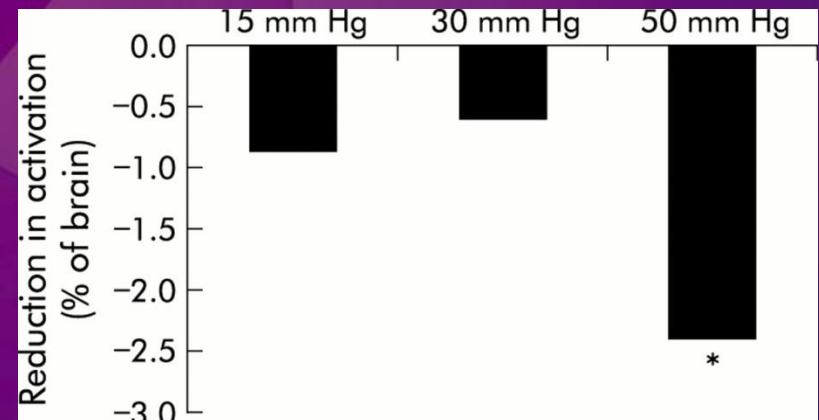
Tricyclic antidepressant ↓ stress-induced visceral hypersensitivity



Net difference in brain activation between placebo and TCA during rectal distension under stress

Left posterior parietal cortex

Perigenual anterior cingulate cortex



Therapist-based psychotherapies are effective

| Psychotherapy | No. of studies | No. of subjects | Relative risk (95% C.I.) of persistent IBS symptoms |
|--------------------------------------|----------------|-----------------------------|---|
| Cognitive behavioural therapy | 9 | 349 (control: 261) | 0.60 (0.44-0.83) |
| Dynamic psychotherapy | 2 | 138 (control: 135) | 0.60 (0.39-0.93) |
| Hypnotherapy | 5 | 141 (control: 137) | 0.74 (0.63-0.87) |
| Multi-component psychotherapy | 5 | 168 (control: 167) | 0.72 (0.62-0.83) |
| Mindfulness meditation training | 1 | 36 (control: 39) | 0.57 (0.32-1.01) |
| Self-administered CBT | 3 | 73 (control: 71) | 0.53 (0.17-1.66) |
| Internet-based CBT | 2 | 71 (control: 69) | 0.75 (0.48-1.17) |
| Relaxation training | 6 | 133 (control: 122) | 0.77 (0.57-1.04) |
| Stress management | 2 | 59 (control: 39) | 0.63 (0.19-2.08) |
| ALL | | 1232 (control: 1102) | 0.68 (0.61-0.76) |

Conflicting results for Chinese Medicine

- Only individualized treatment group has maintained improvement at 14 weeks after completion of treatment

Bensoissan et al. JAMA 1998

- No difference in global or individual IBS symptoms, or quality of life for standardized herbal formula

Leung et al. Am J Gastroenterol 2006

- Acupuncture is not more effective than sham treatment

Manheimer et al. Am J Gastroenterol 2012

Summary

- Clinical diagnosis based on symptom criteria
- Complex pathophysiology implies the need of multi-target treatment
- Antispasmodic remain the 1st line treatment
- Trial of probiotics is safe and may be effective
- Short-term efficacy for low-FODMAP diet and Rifaximin in selected patients
- Good efficacy for SSRIs as off-label use
- Role of new drugs yet to be defined