Functional Abdominal Pain Disorders
Current Treatment Strategies

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History

- 15 y.o. girl, developmentally normal
- Persistent or recurrent pain or discomfort centered in the upper abdomen (above the umbilicus)
- She experiences fullness and bloating especially after the main meal
- There is intermittent nausea and fatty meals worsen the symptoms
- Not relieved by defecation or associated with the onset of a change in stool frequency or stool form
- Clinical exam is normal

Functional dyspepsia

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

- **Postprandial fullness**
- **Early satiation**
- **Epigastric pain or burning not associated with defecation**

- **After appropriate evaluation, the symptoms cannot be fully explained by another medical condition**

Hyams JS, et al. Gastroenterology 2016

Within FD, the following subtypes are now adopted:

- **Postprandial distress syndrome:** bothersome postprandial fullness or early satiation that prevents finishing a regular meal
  - Supportive features: upper abdominal bloating, postprandial nausea, or excessive belching

- **Epigastric pain syndrome,** all of the following: bothersome pain or burning localized to the epigastrium
  - Supportive criteria can include (a) burning quality of the pain, without a retrosternal component and (b) pain commonly induced or relieved by ingestion of a meal but may occur while fasting

Hyams JS, et al. Gastroenterology 2016

History

- 10 y.o. boy, developmentally normal
- Periumbilical abdominal pain every day with radiation to the epigastric region for the past 6 months
- Pain wax and weans, most of the time crampy, sometimes wakes him up at night
- Defecation pattern is completely normal
- No influence of meals
- Tried “everything”
- Missing school

Functional Abdominal Pain Not Otherwise Specified (NOS)

Criteria must be fulfilled at least 4 times per month, at least 2 months before diagnosis and include all of the following:

- **Episodic or continuous abdominal pain that does not occur solely during physiologic events (eg, eating, menses)**
- **Insufficient criteria for IBS, FD, or abdominal migraine**

Hyams JS, et al. Gastroenterology 2016

Irritable bowel syndrome

Must include *all* of the following for at least 2 months before diagnosis:

- **1. Abdominal pain at least 4 days per month associated with one or more of the following:**
  - **a. Related to defecation**
  - **b. A change in frequency of stool**
  - **c. A change in form (appearance) of stool**
- **2. In children with constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not IBS)**
- **Pediatric IBS subtypes reflecting predominant stool pattern (IBS-C, IBS-D, IBS with constipation and diarrhea, and unspecified IBS)**

Hyams JS, et al. Gastroenterology 2016

Abdominal migraine

Must include all of the following occurring at least twice for at least 6 months:

- **Paroxysmal episodes of intense, acute periumbilical, midline or diffuse abdominal pain lasting >1 hour (should be the most severe and distressing symptom)**
- **Episodes are separated by weeks to months**
- **The pain is incapacitating and interferes with normal activities**
- **Stereotypical pattern and symptoms in the individual patient**
- **The pain is associated with 2 or more of the following:**
  - **a. anorexia, b. nausea, c. vomiting, d. headache, e. photophobia, f. Pallor**

Hyams JS, et al. Gastroenterology 2016

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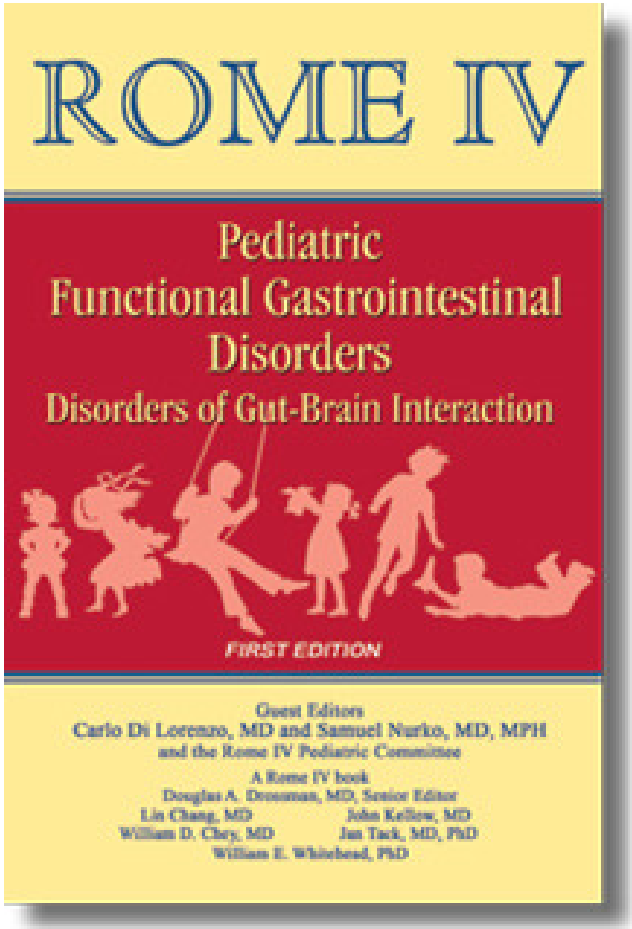
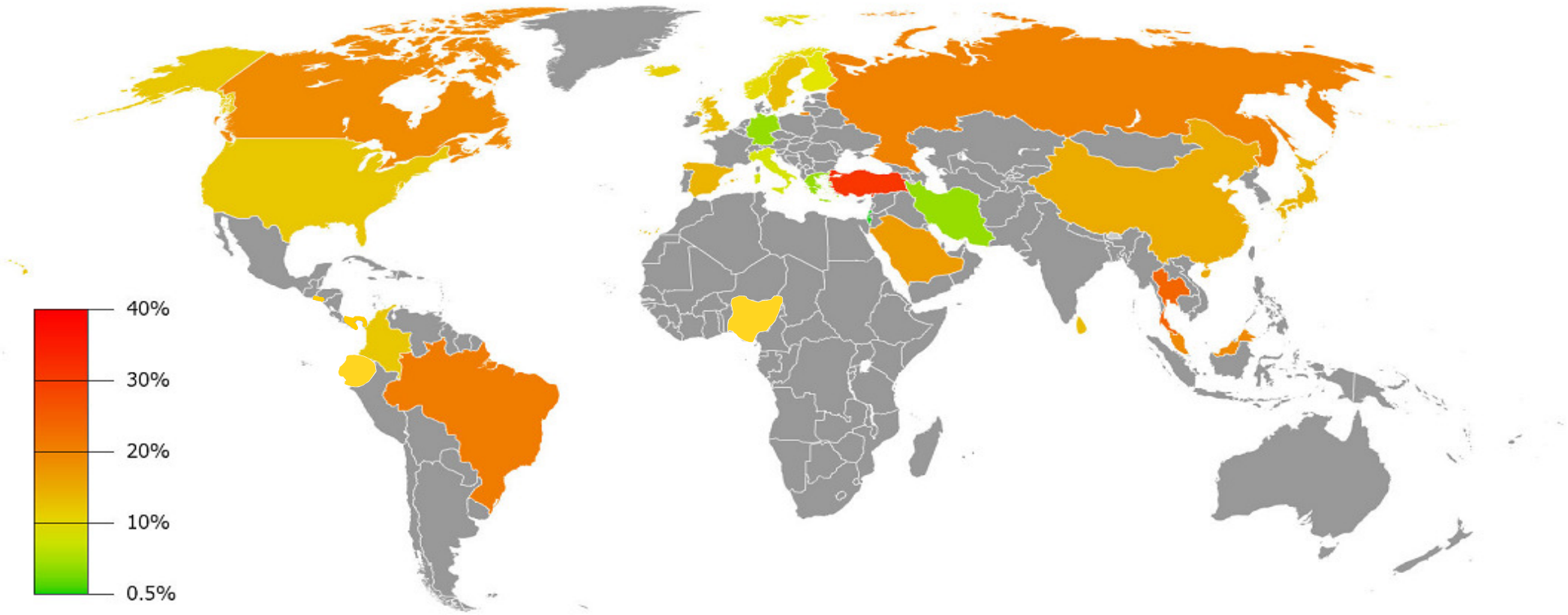
Volume 150, Issue 6

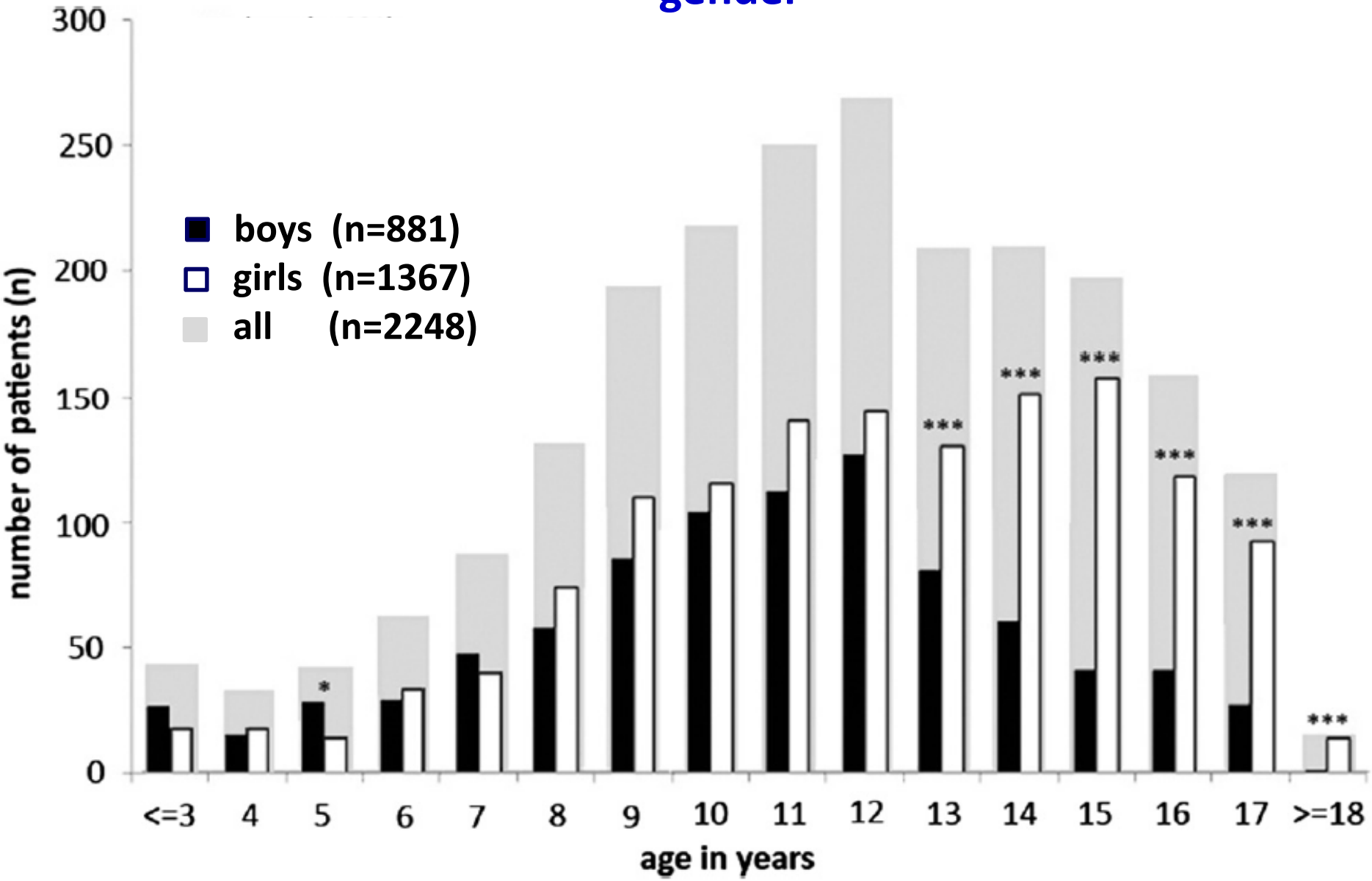


Geographic distribution of functional abdominal pain

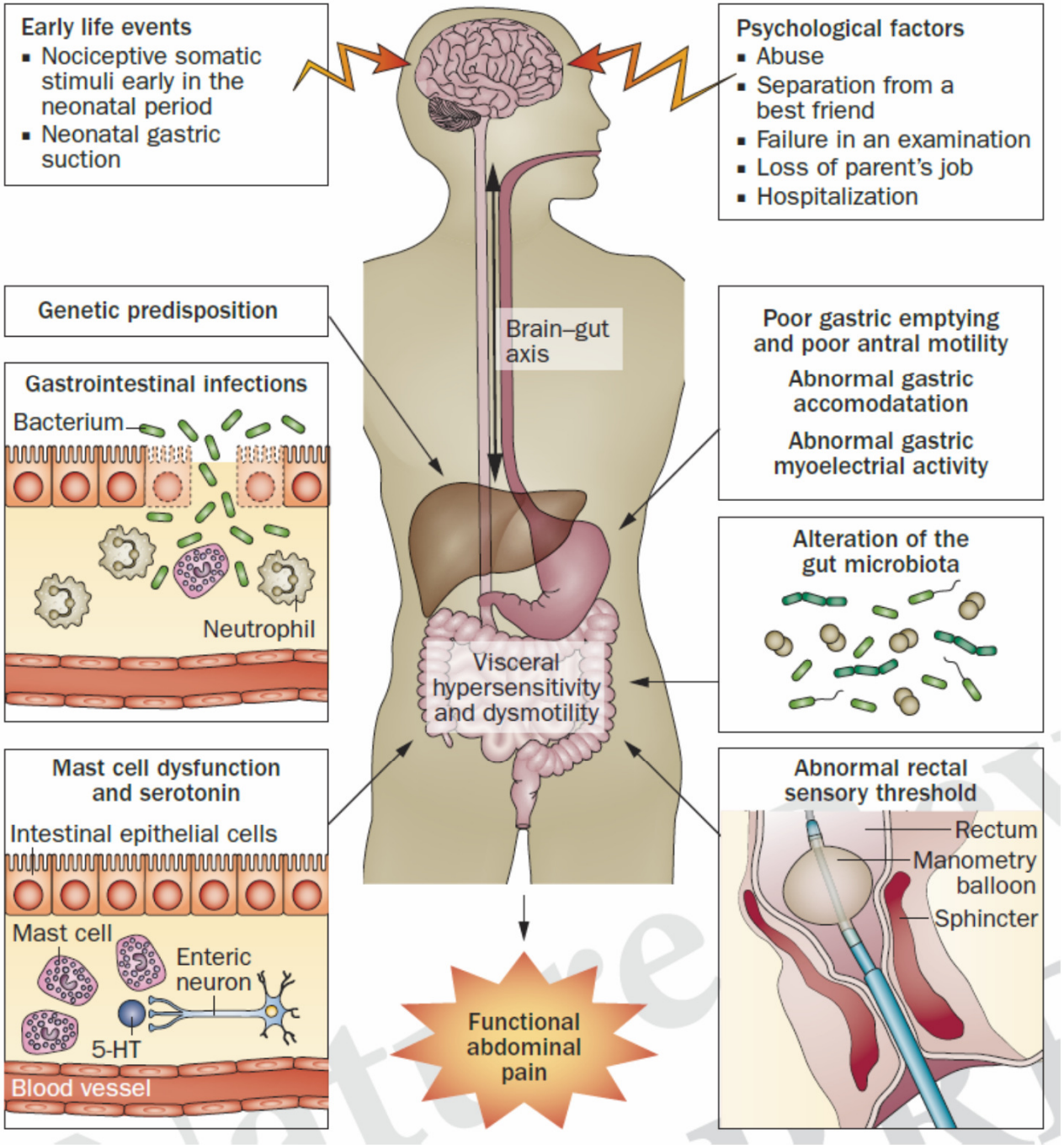


Korterink J, et al. PlosOne 2015

Distribution of children with chronic pain by age and gender



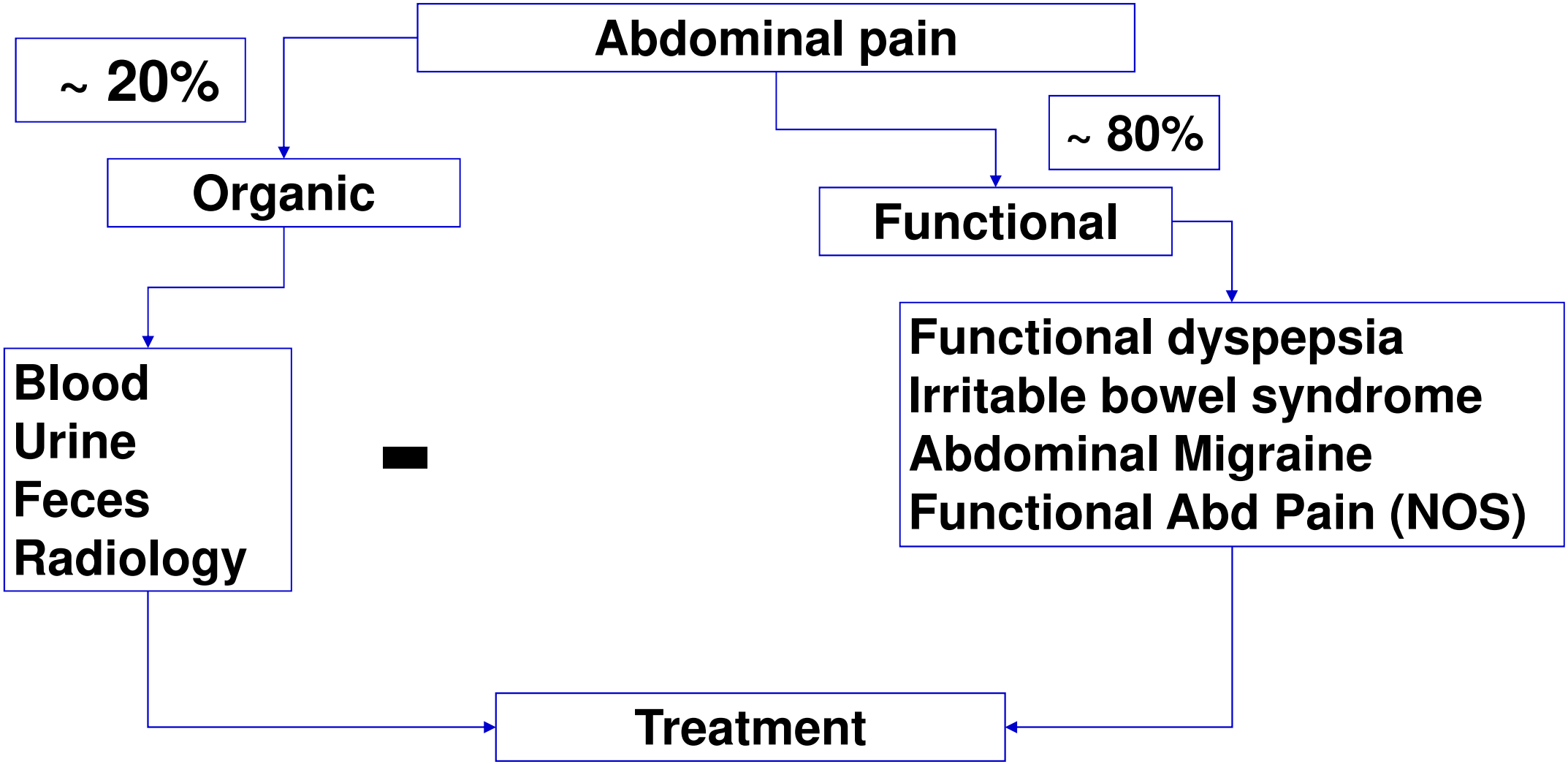
Zernikow B, et al. BMC Pediatrics 2012



Mechanisms Underlying the Irritable Bowel Syndrome (IBS)

Korterink JJ, et al. Nat Rev Gastroenterol Hepatol 2015

Functional abdominal pain disorders



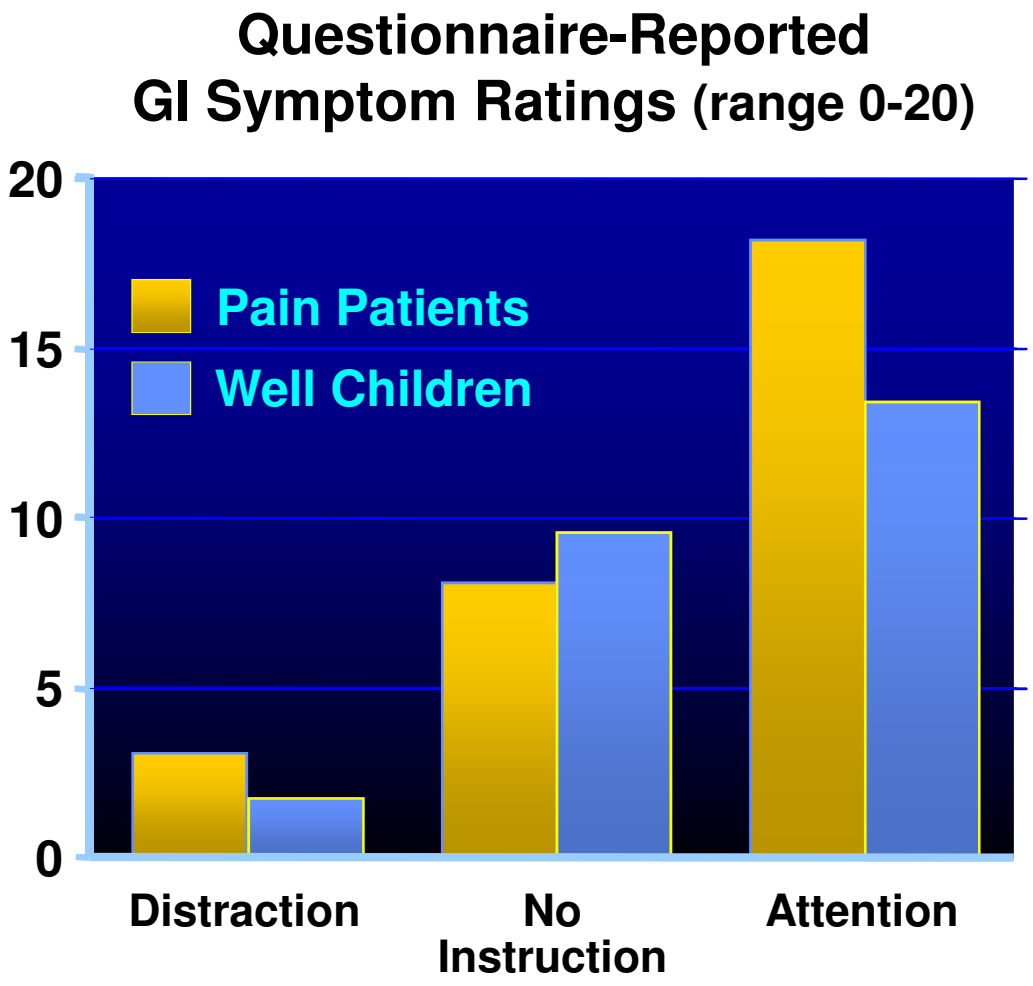
Explain and Reassure

Encourage positive attitude, but realistic expectations

Discuss and reassure

- **Prevalence of FGID**
- **Benign clinical course**
- **Intermittent symptoms likely**
- **Often impact on QoL**
- **Although "cure" unlikely – most patients improve with management**

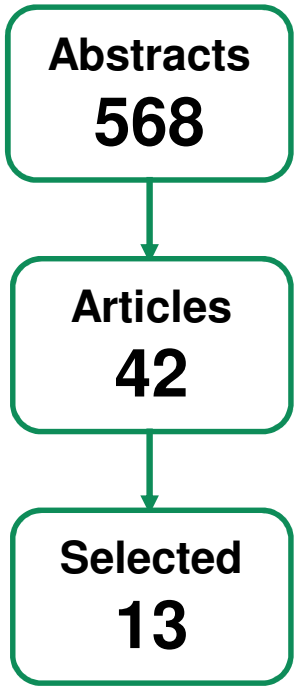
Parent Attention vs. Distraction



- Pain induced by water load test
- Parents randomized to using distraction or attention in their interaction with children in pain
- All mothers felt distraction was inappropriate response to pain

Walker LS, et al. Pain 2006

Nonpharmacologic treatment of functional abdominal pain disorders: a systematic review



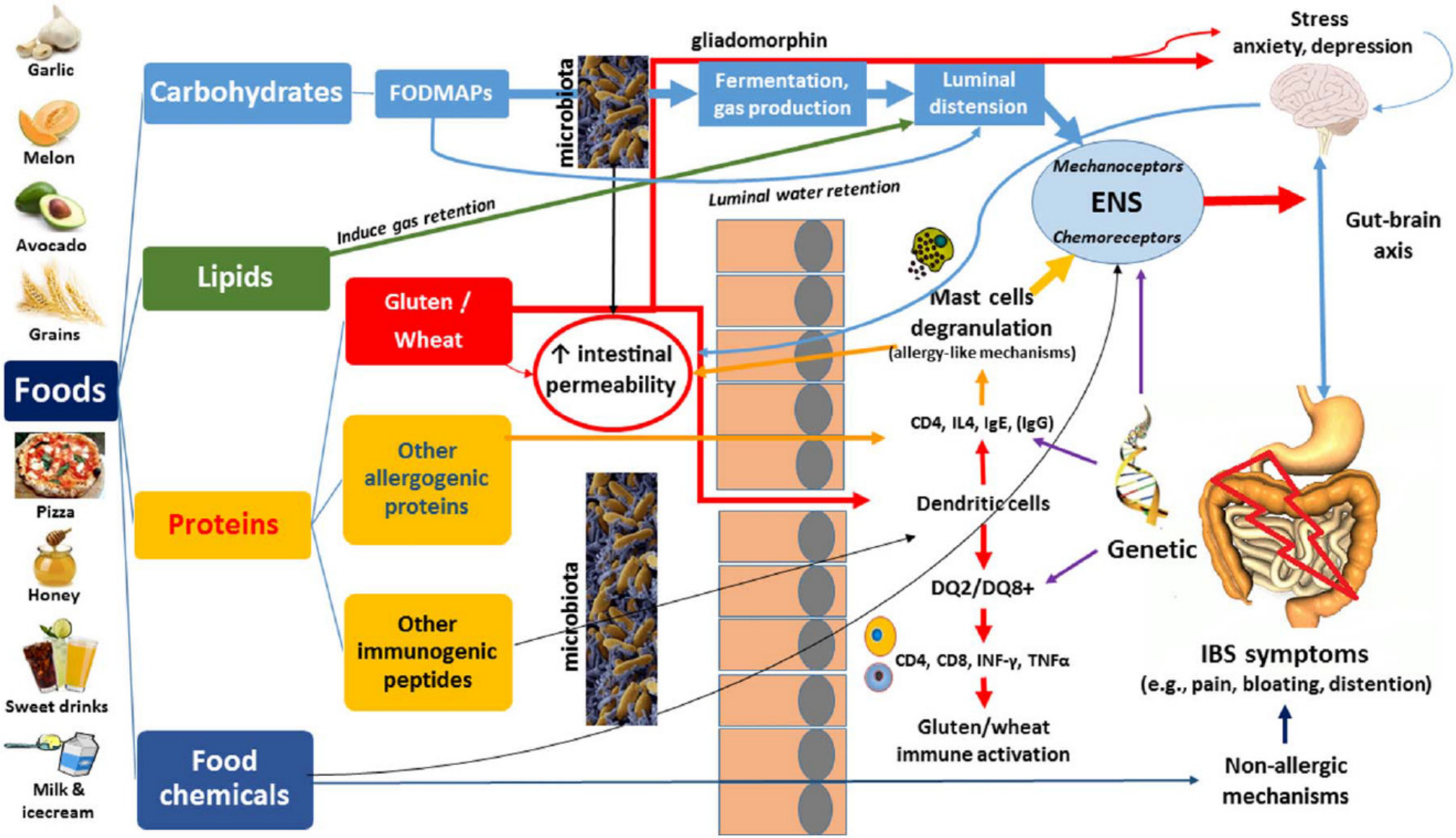
- Removal duplicates, n=316
- Exlusion based on abstract, n=210
- Not meeting inclusion critera, n=29

- 1390 children, aged 3-18 years

- Evaluating fibers, lactose free diet, probiotics, hypnotherapy, cognitive behavior therapy, yoga and written self disclosure

- No studies included on lifestyle, prebiotics, acupunture, massage, gluten-, histamine-, or carbonic acid–free diets and fluid intake

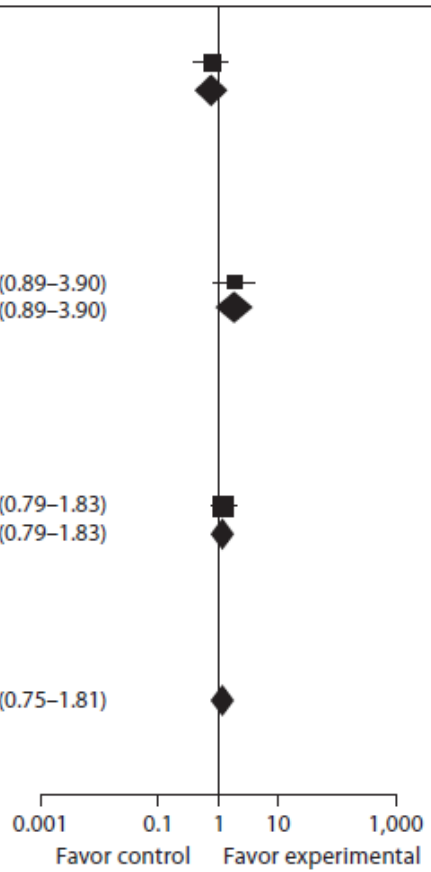
Rutten JM, et al. Pediatrics 2015



Di Giorgo R, et al. Gut 2015

Systematic Review of RCTs: Fiber Supplements for Abdominal Pain-Related FGIDs in Childhood

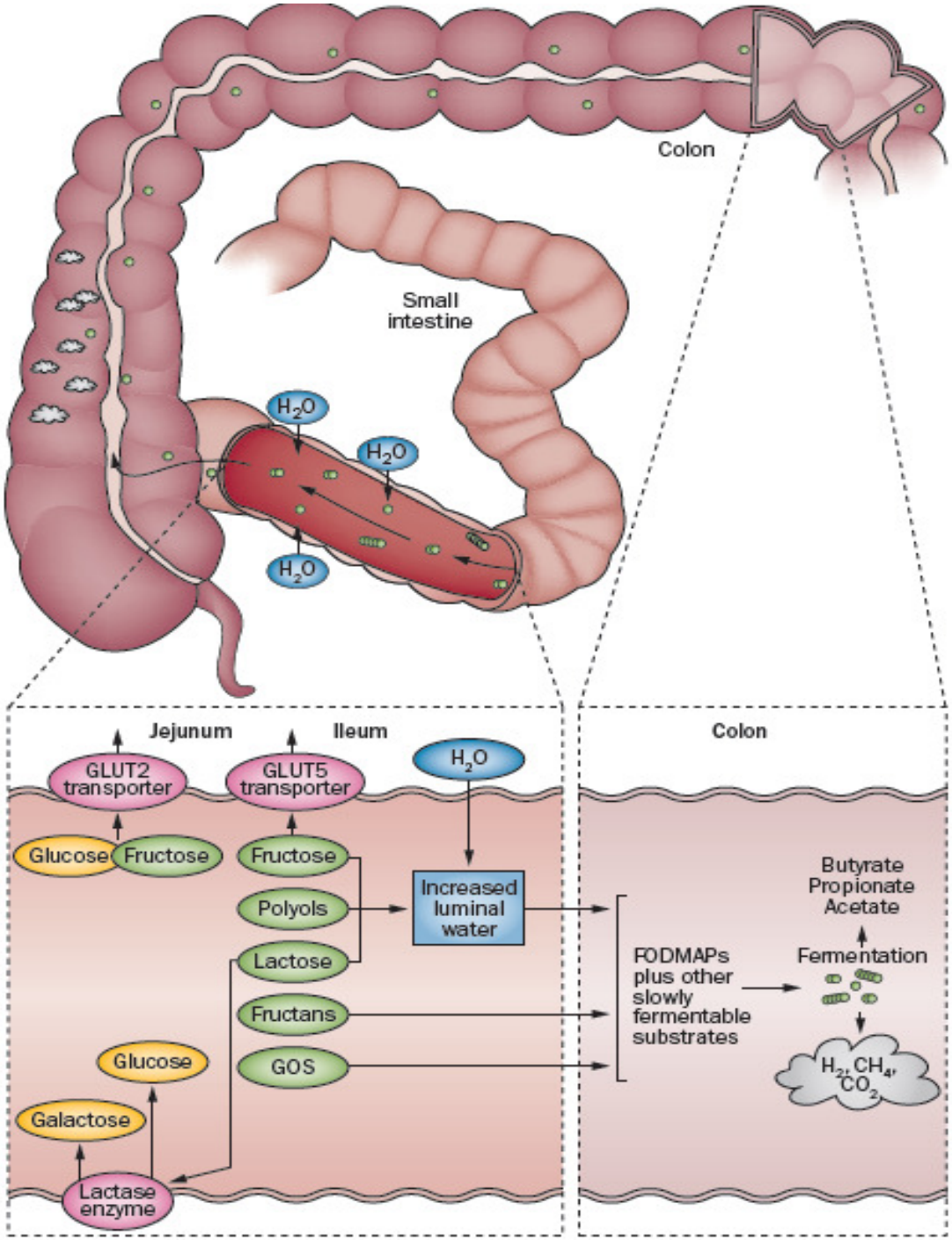
Study or subgroup	Favor experimental events	Favor experimental total	Control events	Control total	Weight %	RR M-H, random (95% CI)
2.2.1 Crushed crispbread with 66% fiber [Ispaghula husk]						
Christensen [16], 1982	7	15	10	16		
Subtotal (95% CI)		15		16		
Total events	7		10			
Heterogeneity: not applicable						
Test for overall effect: Z = 0.87 (p = 0.39)						
2.2.2 Fiber cookies [corn fiber]						
Feldman et al. [17], 1985	13	26	7	26	24.6	1.86 (0.89–3.90)
Subtotal (95% CI)		26		26	24.6	1.86 (0.89–3.90)
Total events	13		7			
Heterogeneity: not applicable						
Test for overall effect: Z = 1.64 (p = 0.10)						
2.2.3 Glucomannan						
Horvath et al. [25], 2011	23	41	20	43	46.8	1.21 (0.79–1.83)
Subtotal (95% CI)		41		43	46.8	1.21 (0.79–1.83)
Total events	23		20			
Heterogeneity: not applicable						
Test for overall effect: Z = 0.88 (p = 0.38)						
Total (95% CI)		82		85	100.0	1.17 (0.75–1.81)
Total events	43		37			
Heterogeneity: $\tau^2 = 0.66$; $\chi^2 = 3.33$, d.f. = 2 (p = 0.19); $I^2 = 40\%$						
Test for overall effect: Z = 0.70 (p = 0.49)						

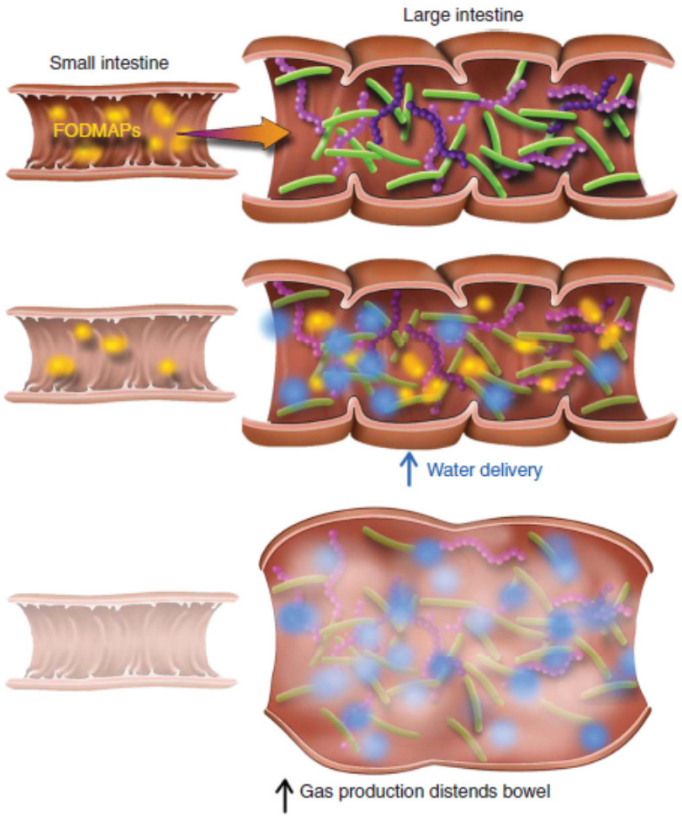


Horvath A, et al. Ann Nutr Metab 2012

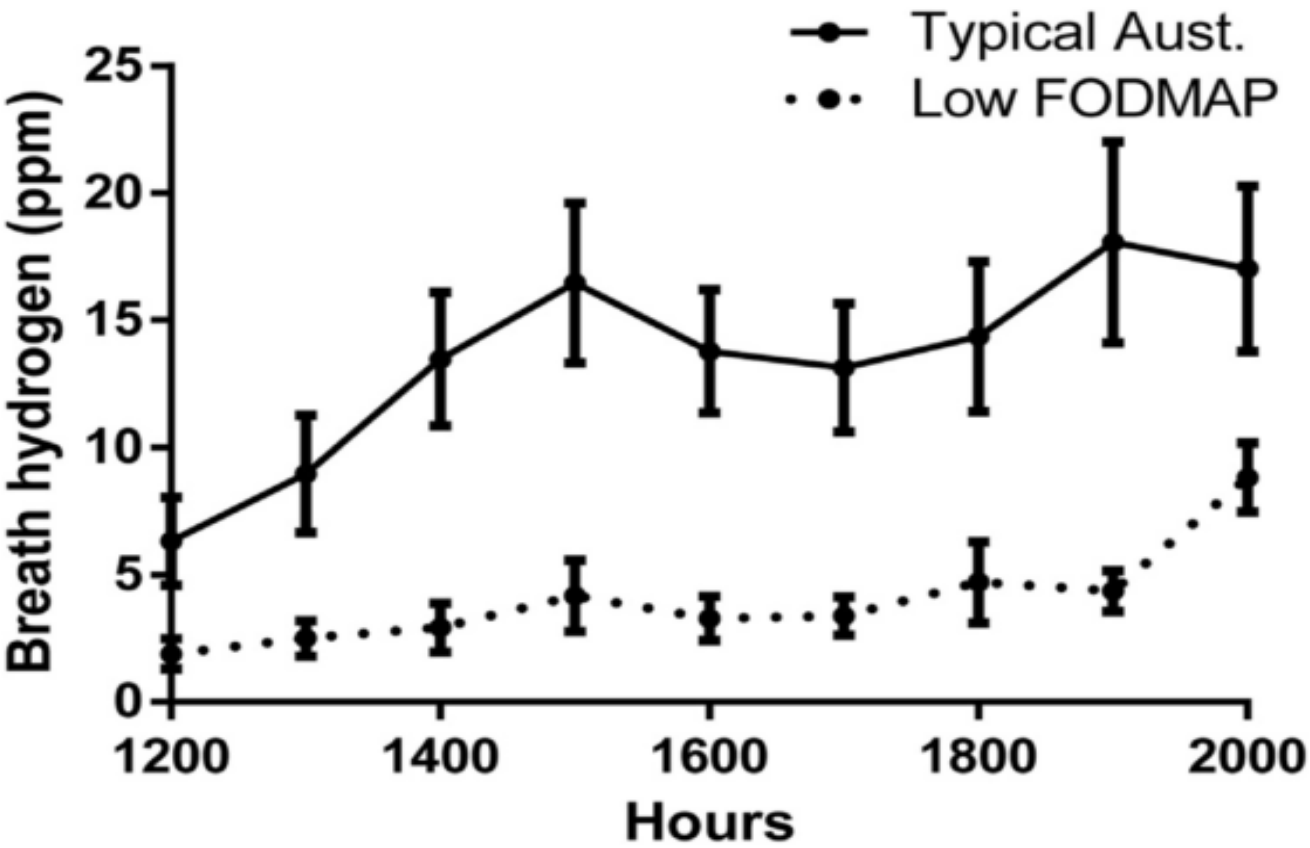
FODMAP

- **F**ermentable
- **O**ligosaccharides (fructans, (FOS and GOS))
- **D**isaccharides (lactose)
- **M**onosaccharides (fructose)
- **A**nd
- **P**olyols (sugar alcohols)
  - artificial sweeteners sorbitol, mannitol, maltitol, and xylitol


Colon
Small intestine
H_2O
H_2O
H_2O
Jejunum
Ileum
Colon
GLUT2 transporter
GLUT5 transporter
H_2O
Glucose
Fructose
Fructose
Polyols
Increased luminal water
Lactose
Fructans
GOS
Glucose
Galactose
Lactase enzyme
FODMAPs plus other slowly fermentable substrates
Fermentation
Butyrate
Propionate
Acetate
H_2, CH_4, CO_2

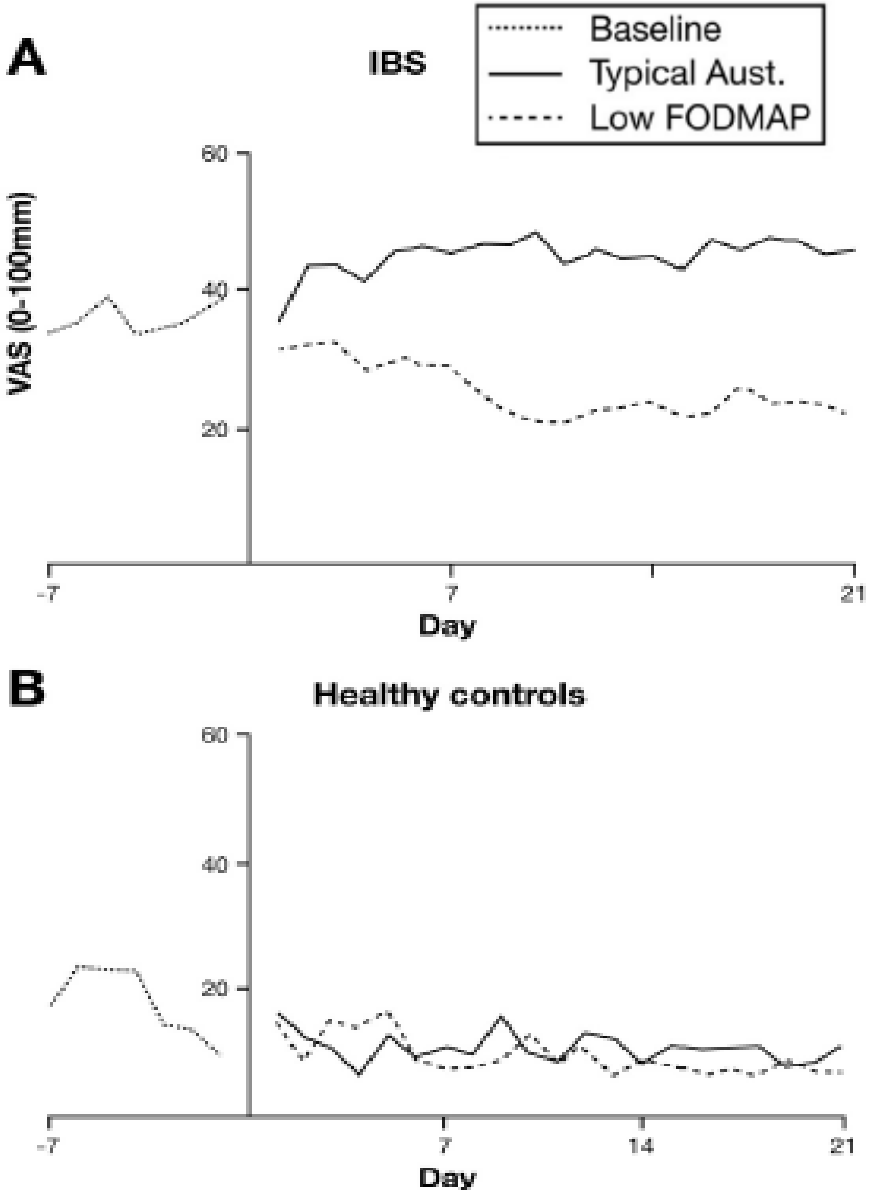

Large intestine
Small intestine
FODMAPs
Water delivery
Gas production distends bowel

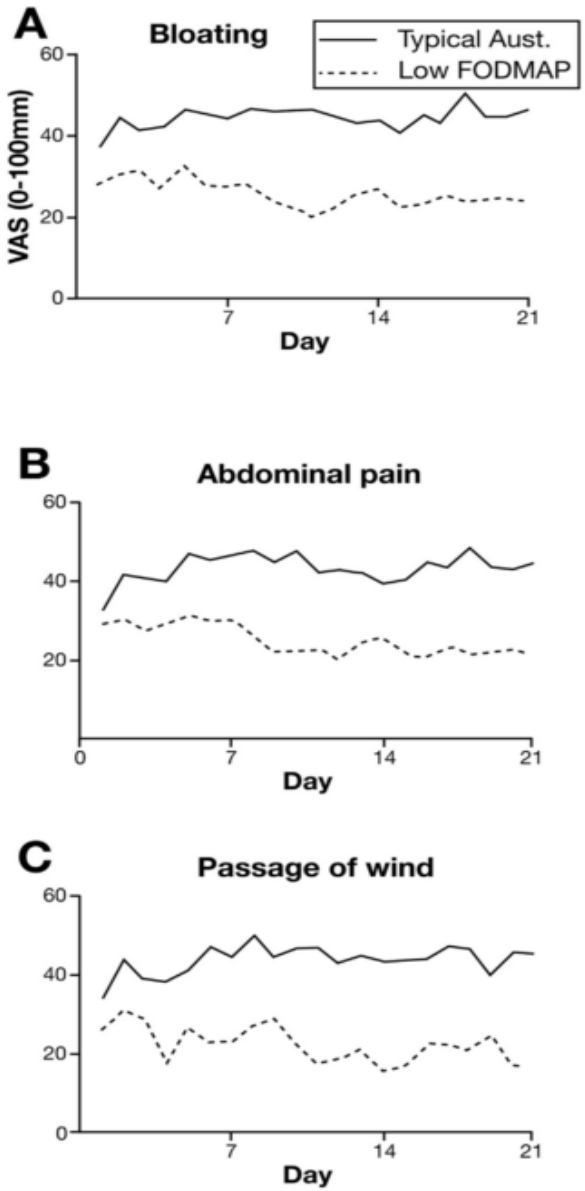
Breath hydrogen test Typical Australian diet versus Low FODMAP diet



Halmos AP, et al. Gastroenterology 2014

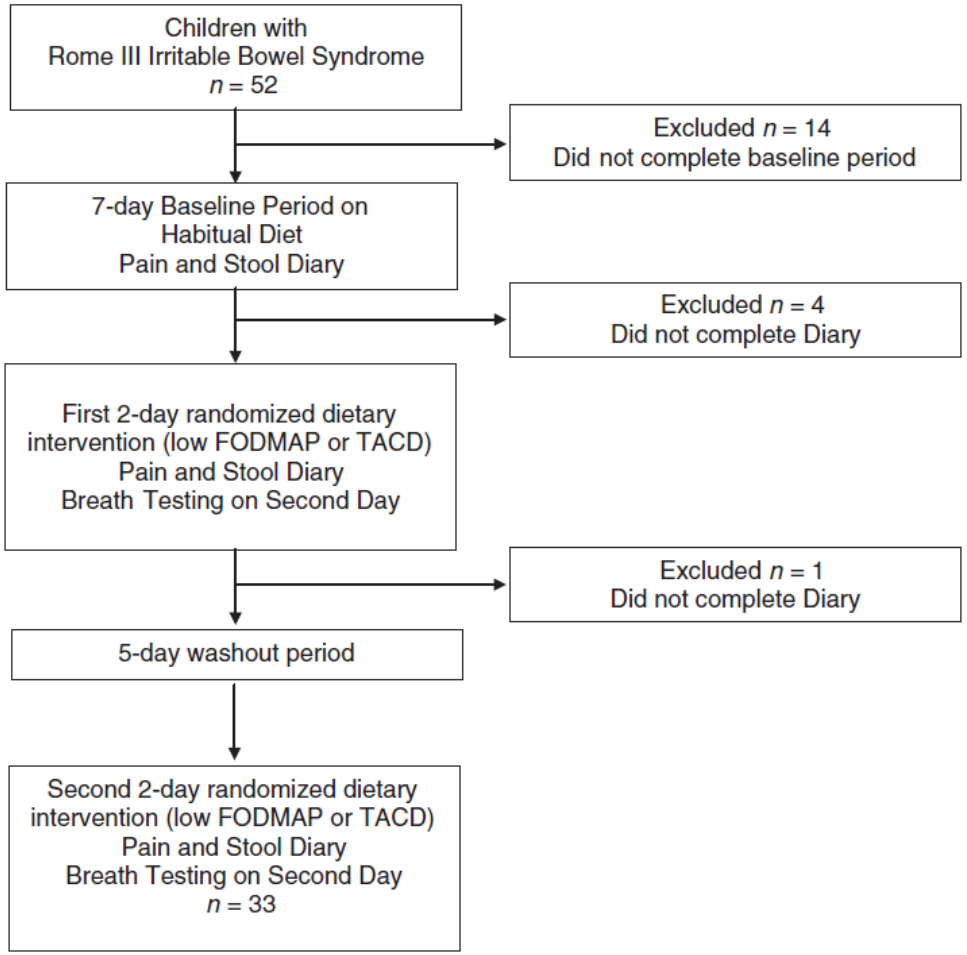
Gastrointestinal symptoms during different diets





Halmos AP, et al. Gastroenterology 2014

RCT: gut microbiome biomarkers are associated with clinical response to a low FODMAP diet in children with IBS

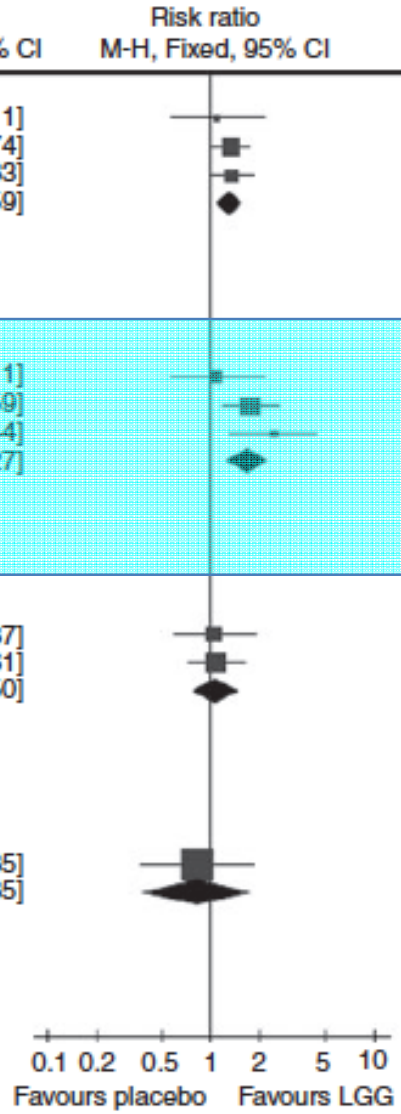


- **Less abdominal pain occurred during the low FODMAP diet vs. TACD [1.1 episodes/day vs. 1.7 P < 0.05]**
- **Compared to baseline (1.4 0.2), children had fewer daily abdominal pain episodes during the low FODMAP diet (P < 0.01) more episodes during the TACD (P < 0.01)**

Chumpitazi BP, et al. Aliment Pharmacol & Ther 2015

Effect of Lactobacillus GG on responder rates
(defined as no pain or a decrease in pain intensity)

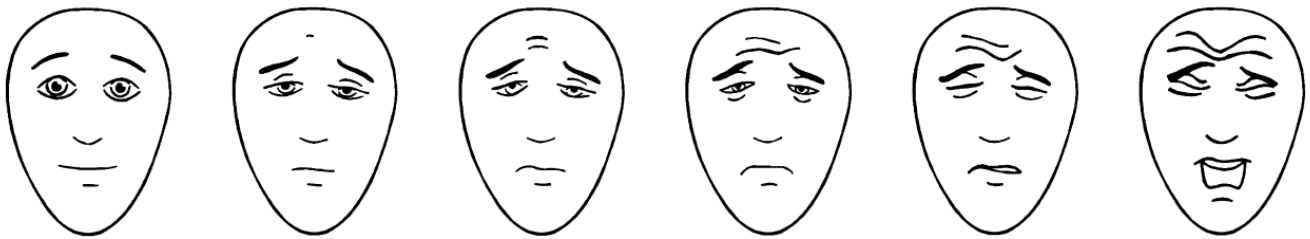
Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, Fixed, 95% CI
1.1.1 Overall						
Bausserman 2005	11	25	10	25	13.4%	1.10 [0.57, 2.11]
Francavilla 2010	48	67	37	69	49.0%	1.34 [1.02, 1.74]
Gawronska 2007	38	52	28	52	37.6%	1.36 [1.00, 1.83]
Subtotal (95% CI)		144		146	100.0%	1.31 [1.08, 1.59]
Total events	97		75			
Heterogeneity: $\chi^2 = 0.35$, df = 2 ($P = 0.84$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.77$ ($P = 0.006$)						
1.1.2 Irritable bowel syndrome						
Bausserman 2005	11	25	10	25	28.9%	1.10 [0.57, 2.11]
Francavilla 2010	33	42	17	38	51.5%	1.76 [1.19, 2.59]
Gawronska 2007	16	18	7	19	19.6%	2.41 [1.31, 4.44]
Subtotal (95% CI)		85		82	100.0%	1.70 [1.27, 2.27]
Total events	60		34			
Heterogeneity: $\chi^2 = 3.00$, df = 2 ($P = 0.22$); $I^2 = 33\%$						
Test for overall effect: $Z = 3.56$ ($P = 0.0004$)						
1.1.3 Functional abdominal pain						
Francavilla 2010	12	25	14	31	44.9%	1.06 [0.61, 1.87]
Gawronska 2007	17	24	15	23	55.1%	1.09 [0.73, 1.61]
Subtotal (95% CI)		49		54	100.0%	1.08 [0.77, 1.50]
Total events	29		29			
Heterogeneity: $\chi^2 = 0.00$, df = 1 ($P = 0.95$); $I^2 = 0\%$						
Test for overall effect: $Z = 0.43$ ($P = 0.67$)						
1.1.4 Functional dyspepsia						
Gawronska 2007	5	10	6	10	100.0%	0.83 [0.37, 1.85]
Subtotal (95% CI)		10		10	100.0%	0.83 [0.37, 1.85]
Total events	5		6			
Heterogeneity: Not applicable						
Test for overall effect: $Z = 0.45$ ($P = 0.66$)						



Horvath A, et al. Aliment Pharmacol Ther 2011

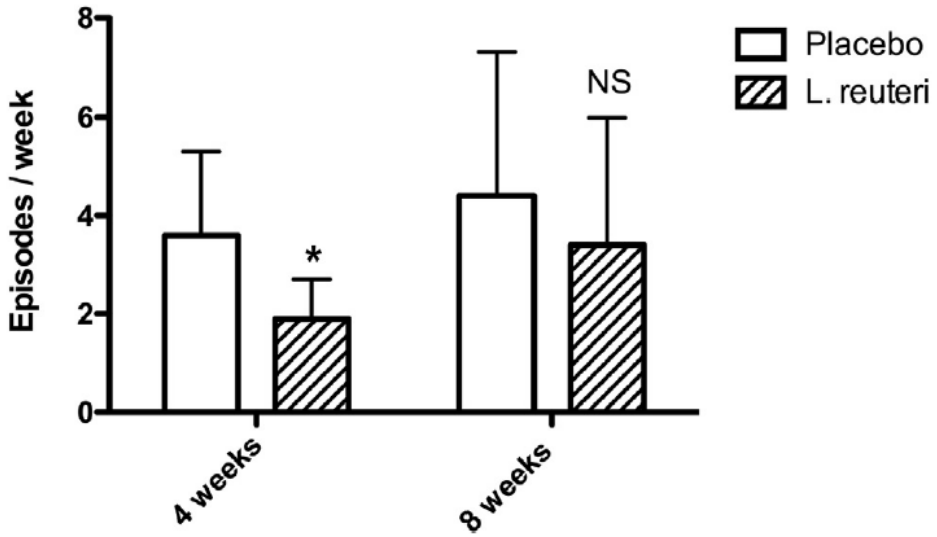
Lactobacillus reuteri DSM 17938 for the Management of Functional Abdominal Pain: A RDBPCT

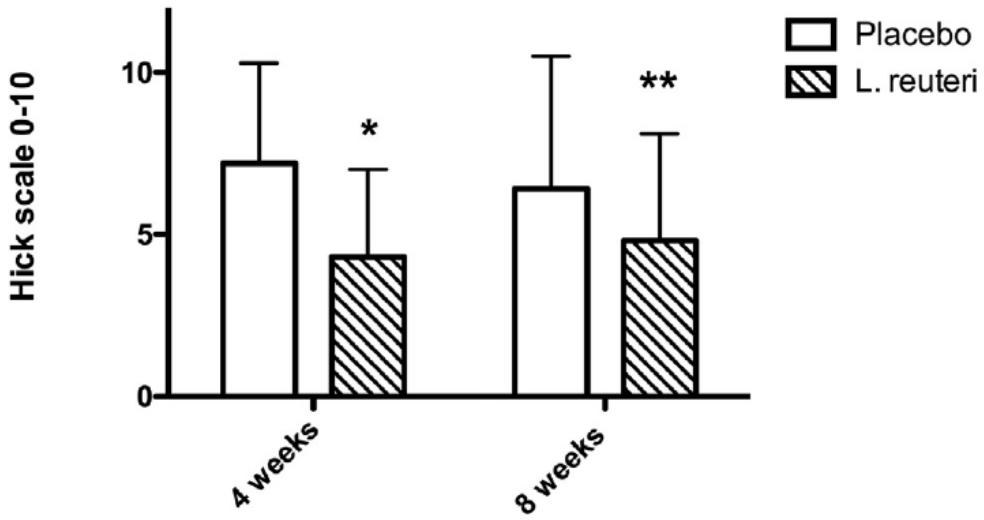
- L reuteri DSM 17938, stimulates gastrointestinal motility and reduction of pain perception
- 101 children, aged 6-15 years, Rome III criteria for FAP
- Randomly assigned to receive either L reuteri DSM 17938 or placebo (tablets) for 4 weeks, with further follow-up of additional 4 weeks



Weizman Z, et al. J Pediatr 2016
Hicks CL, et al. Pain 2001

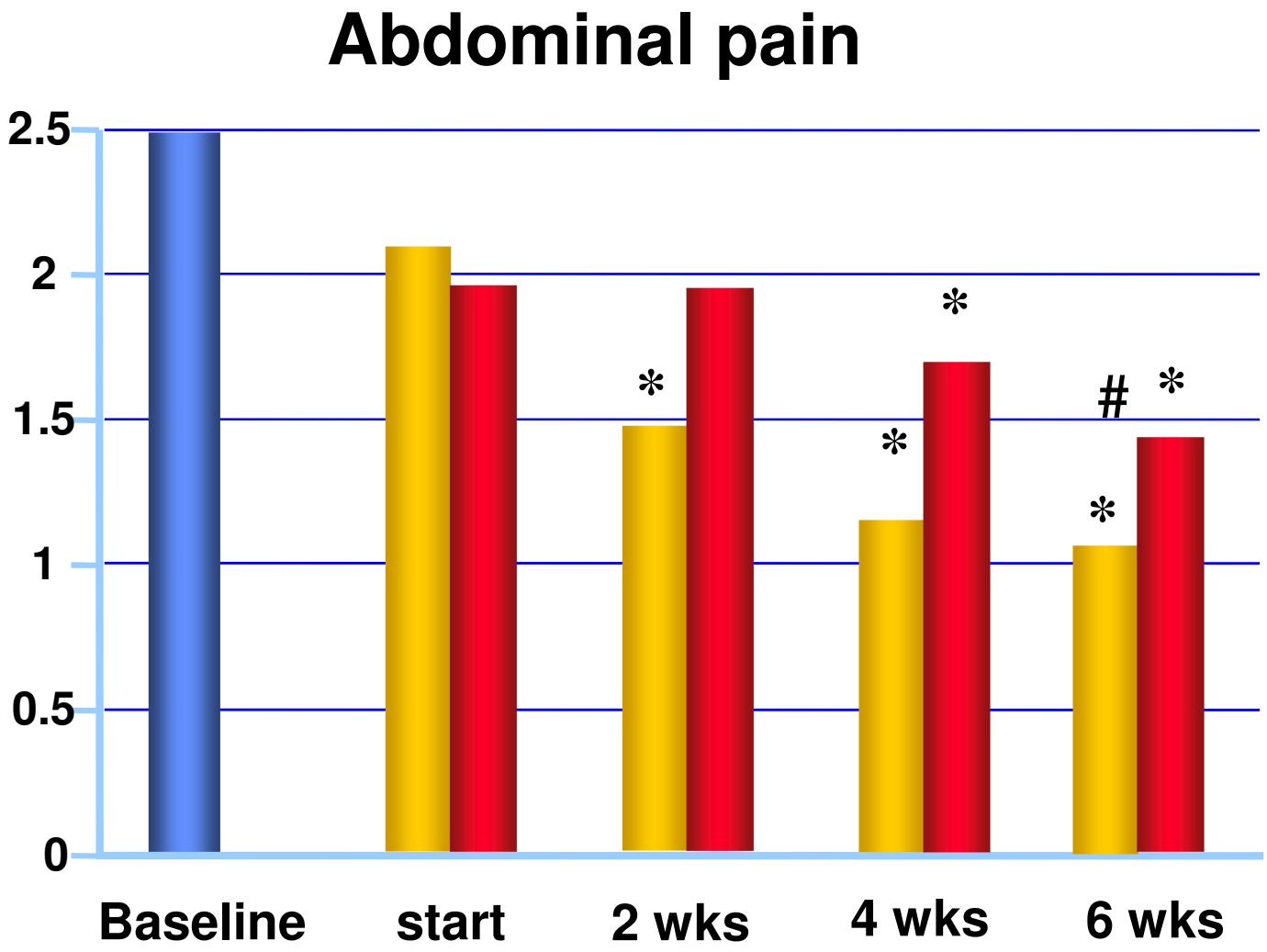
Lactobacillus reuteri DSM 17938 for the Management of Functional Abdominal Pain in Childhood: A RDBPCT





Weizman Z, et al. J Pediatr 2016
Hicks CL, et al. Pain 2001

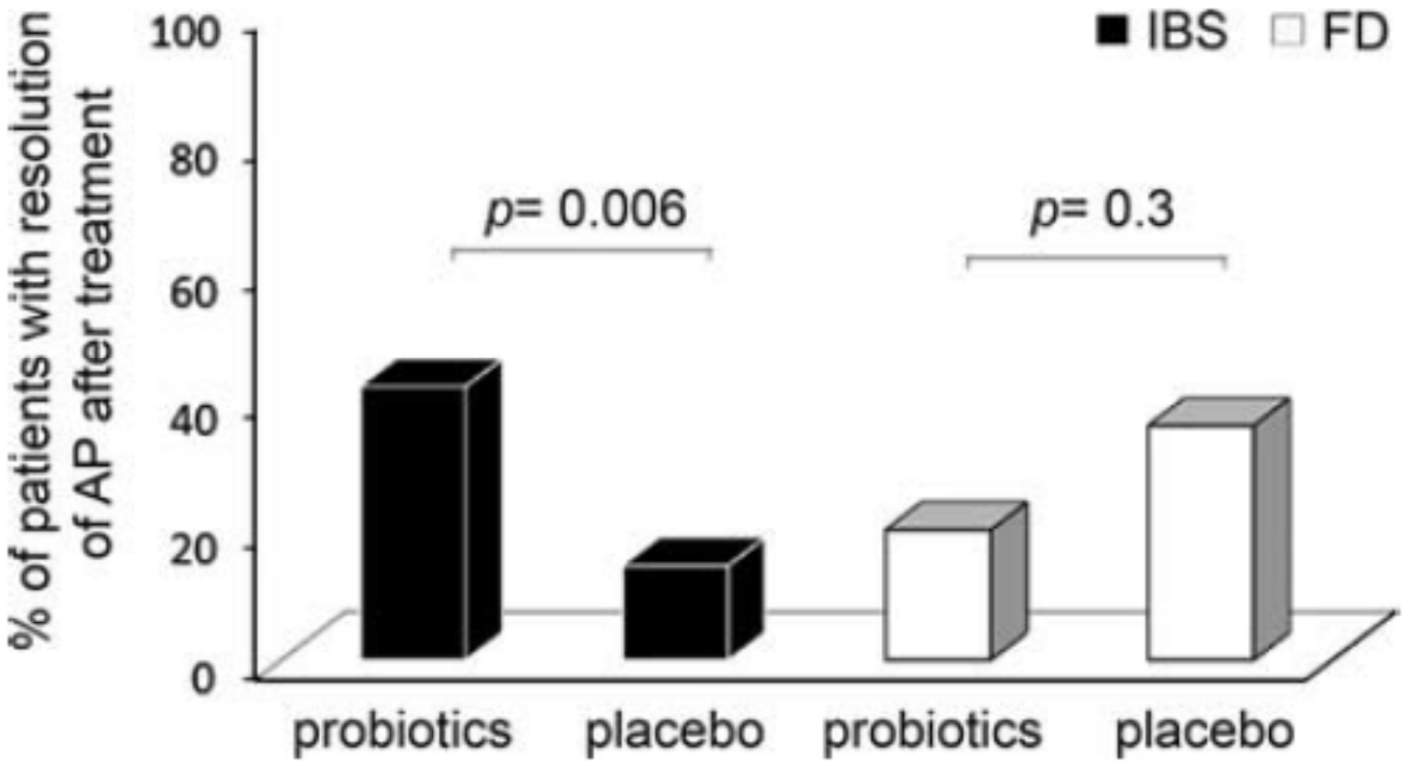
VSL#3 Improves Symptoms in Children with IBS: A Multicenter, DBRP cross-over Study



59 children (5-18 yrs)

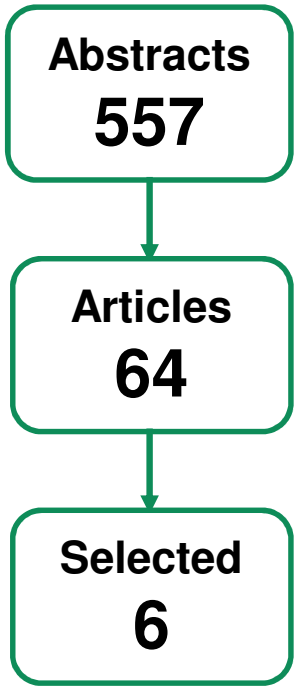
Guandalini S, et al. JPGN 2010

A Mixture of 3 Bifidobacteria Decreases Abdominal Pain and Improves the QoL in Children With IBS. A Multicenter, RDB Placebo-Controlled, Crossover Trial



Gianetti E, et al. J Clin Gastroenterol 2016

Pharmacologic treatment of functional abdominal pain disorders: a systematic review



- Removal duplicates, n=247
- Exlusion based on abstract, n=246
- Not meeting inclusion critera, n=58

- 275 children, aged 4,5-18 year

- Evaluating antispasmodic, antidepressant, antireflux, antihistaminic, and laxative agents

- No studies included on antidiarrheal agents, antibiotics, pain medication, anti-emetics, and antimigraine agents

Korterink JJ, et al. J Pediatr 2015

Antispasmodics

Kline 2001	N=50, 8-17y IBS	2 weeks pepermint oil vs. placebo	GRADE: very low

- Improvement in severity of symptoms: 71% vs. 19% ($p<0.001$)
- No adverse effects reported
- Quality:
  - No concealment of allocation
  - Attrition bias
  - Small sample size

Kline RM, et al. J Pediatr 2001

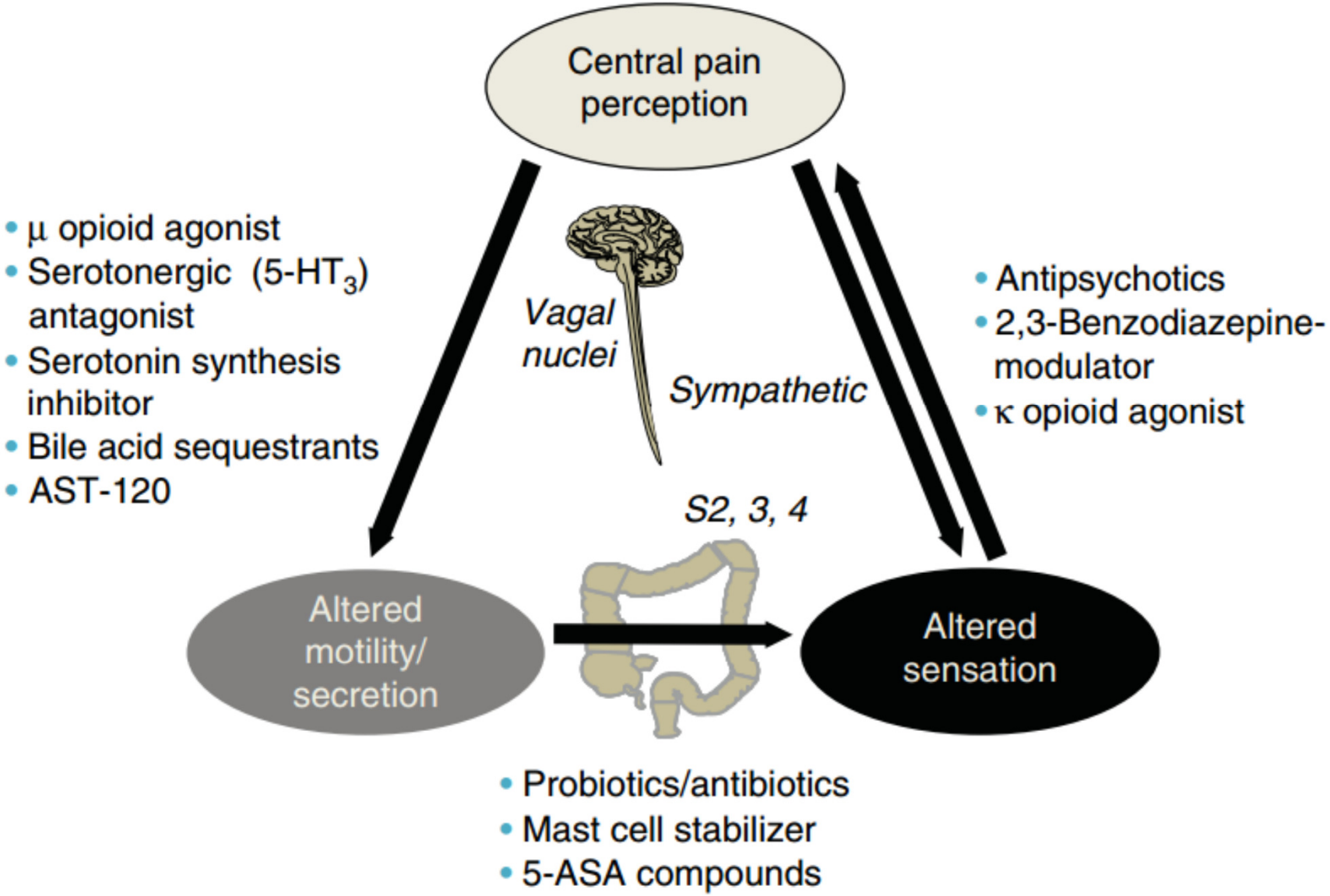
Laxatives

Khoshoo 2006	N=29, 4.5-12y FAP	4 weeks PEG 3350 vs PEG 3350 + tegaserod	GRADE: very low

- Adequate pain reduction (66.7% vs 18.5%; $P < 0.05$) (RR 3.60: 95% CI 1.54-8.40)
- Associated with serious cardiovascular ischemic events
- Quality:
  - No blinding
  - Not placebo controlled
  - Small sample size

Khoshoo V, et al. AP&T 2006

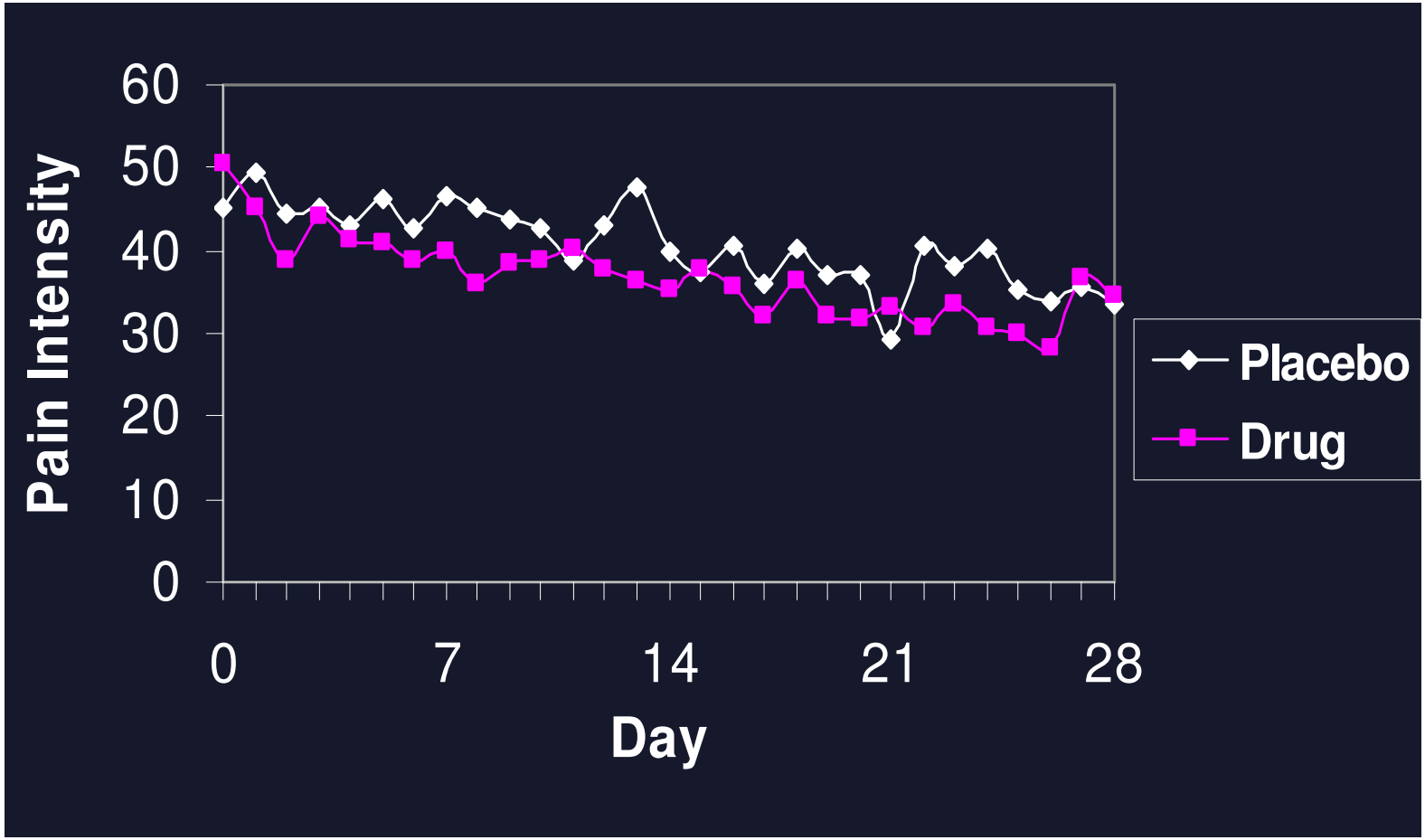
Sites of actions of current medications and novel agents in development for treatment of IBS-D



Camilleri M, Expert Opin Pharmacother 2013

Amitriptyline vs placebo

90 children,
5 centers,
4 wks rx,
5 years to
complete it



- Significant decrease in pain ($p<0.0001$)
- No difference in trend between groups ($p=0.90$)

Overall assessment
Intention to treat

	Total	Placebo		Amitriptyline	
Failed	16%	16 %		15 %	
Poor	11%	7 %		15 %	
Fair	18 %	23 %		13 %	
Good	37 %	39 %	46 %	35 %	50 %
Excellent	11 %	7 %		15 %	

Saps M, et al. Gastroenterology 2009

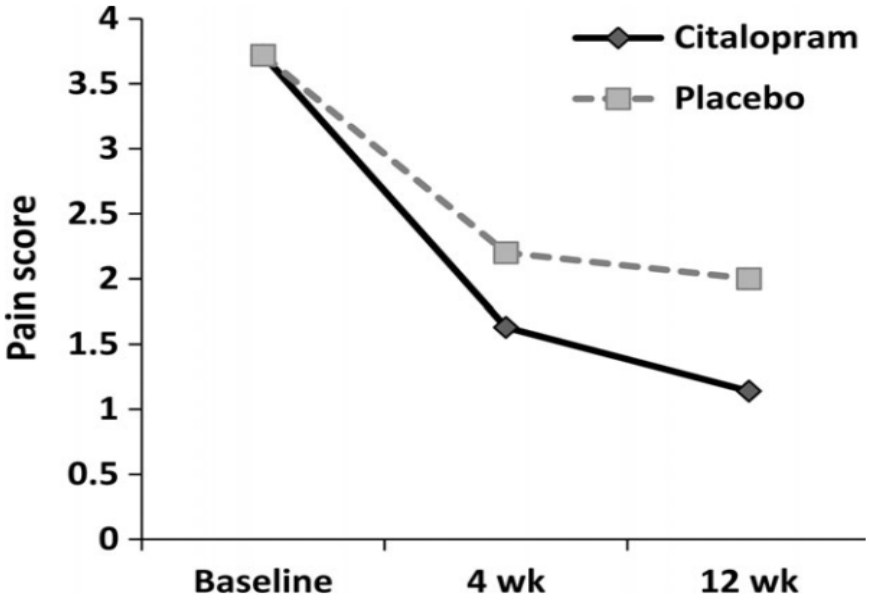
Citalopram (SSRI) for pediatric functional abdominal pain: a randomized, placebo-controlled trial

- 115 children with FAP (Rome III criteria), aged 6–18 yrs
- Citalopram 20 mg/day or placebo for 4 weeks
- Treatment response: ≥2 point reduction in the 6-point Faces pain rating scale or 'no pain'

Roohafza H, et al. Neurogastroenterol Motil 2014

Citalopram 20mg/d for pediatric functional abdominal pain a placebo controlled trial (n =115)

NS



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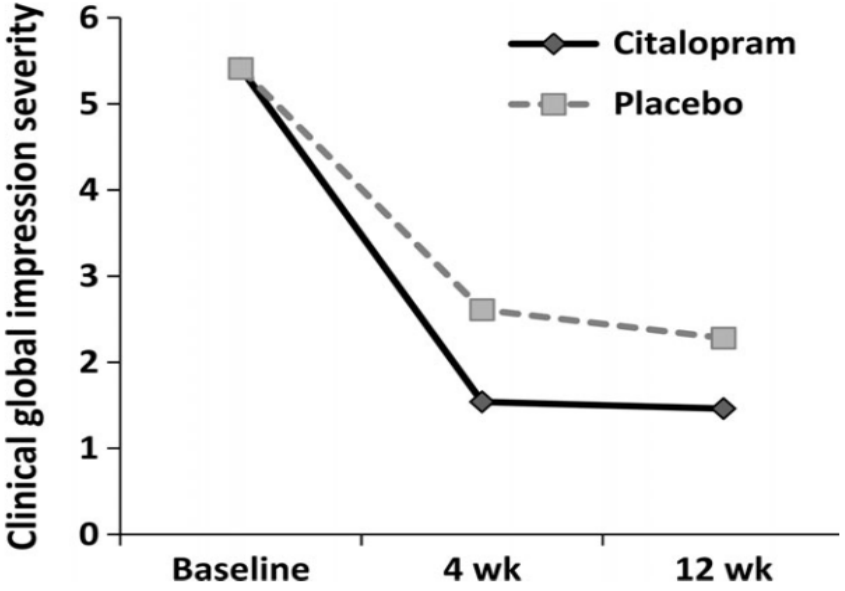


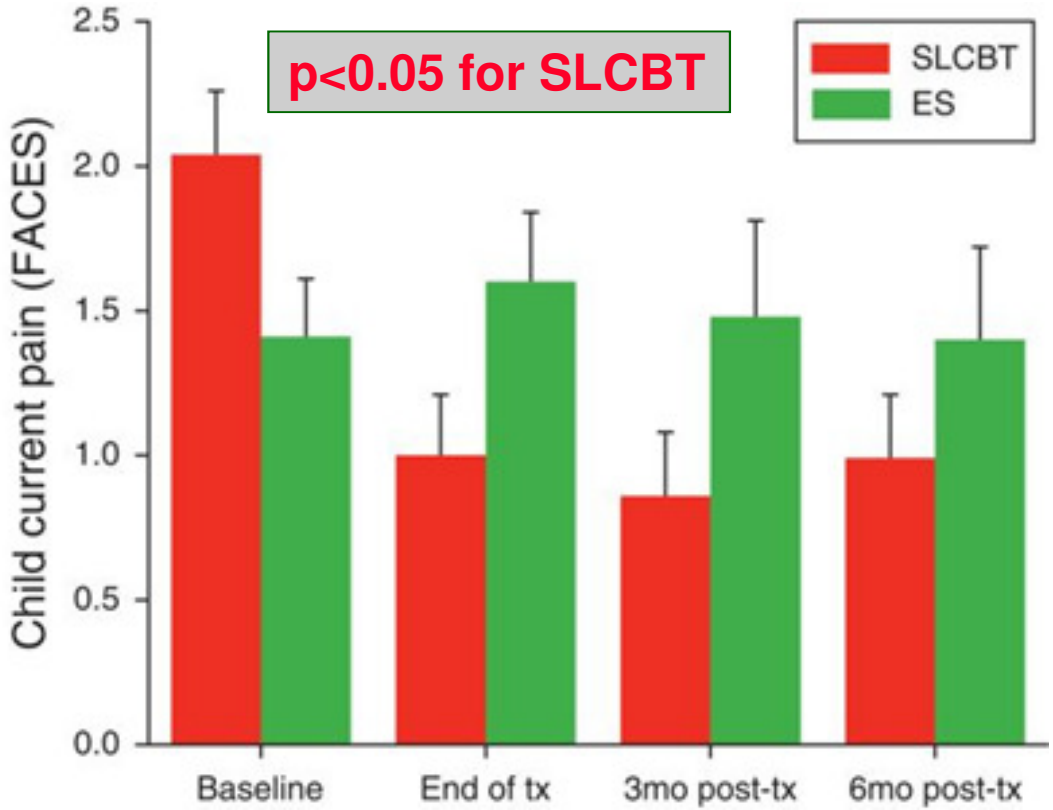
Roohafza H, et al. Neurogastroenterol Motil 2014

Social learning CBT vs Education support: parents-children

- 200 children (7-17) with Apley critera for abdominal pain for at least 3 months
- 3-session intervention of cognitive-behavioral treatment targeting parents' responses to their children's pain complaints and children's coping responses
  - Relaxation training
  - Working with parent and child to modify family responses
  - Cognitive restructuring

Levy RL, et al. Am J Gastroenterol 2010

Social learning CBT vs Education support: parents-children



Levy RL, et al. Am J Gastroenterol 2010

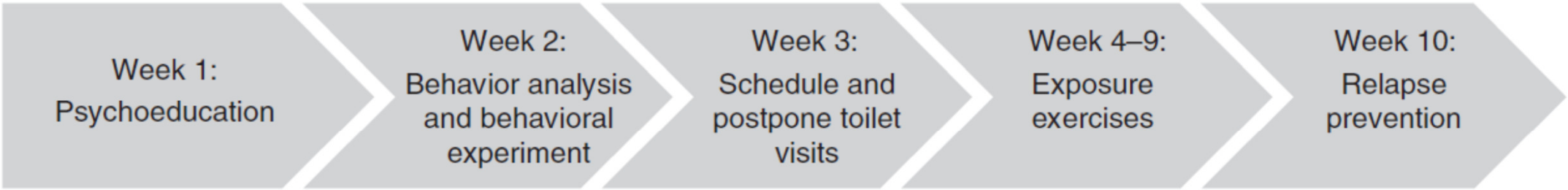
Internet-Delivered Cognitive Behavior Therapy for Adolescents With Irritable Bowel Syndrome: A RCT

- 101 adolescents (13-17) fulfilling Rome III criteria
- Internet-CBT 10-week intervention, main component exposure to IBS symptoms by reduction of avoidance of abdominal symptoms and instead stepwise provocation of symptoms
- Wait-list
- Primary outcome total score on Gastroint Sympt Rating
- Secondary outcomes adolescent- and parent-rated QoL and parent-rated gastrointestinal symptoms

Bonnert M, et al. Am J Gastroenterol 2016

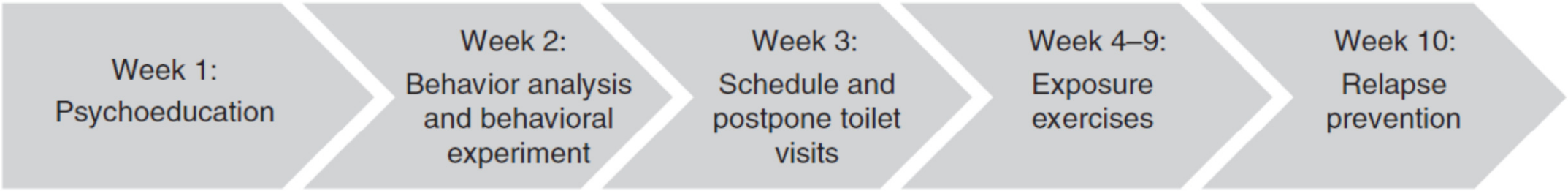
Internet-CBT

Adolescent treatment

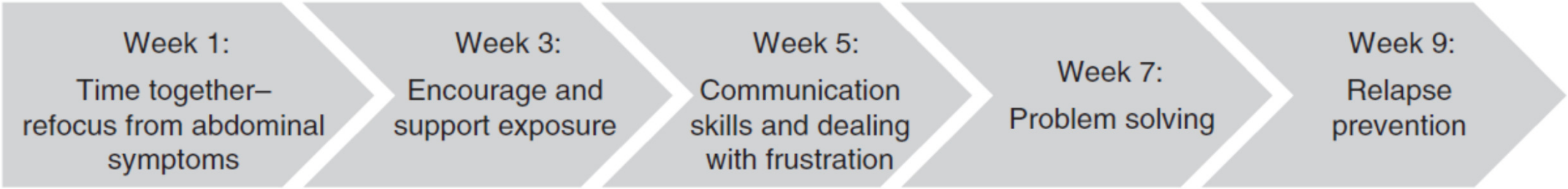


Internet-CBT

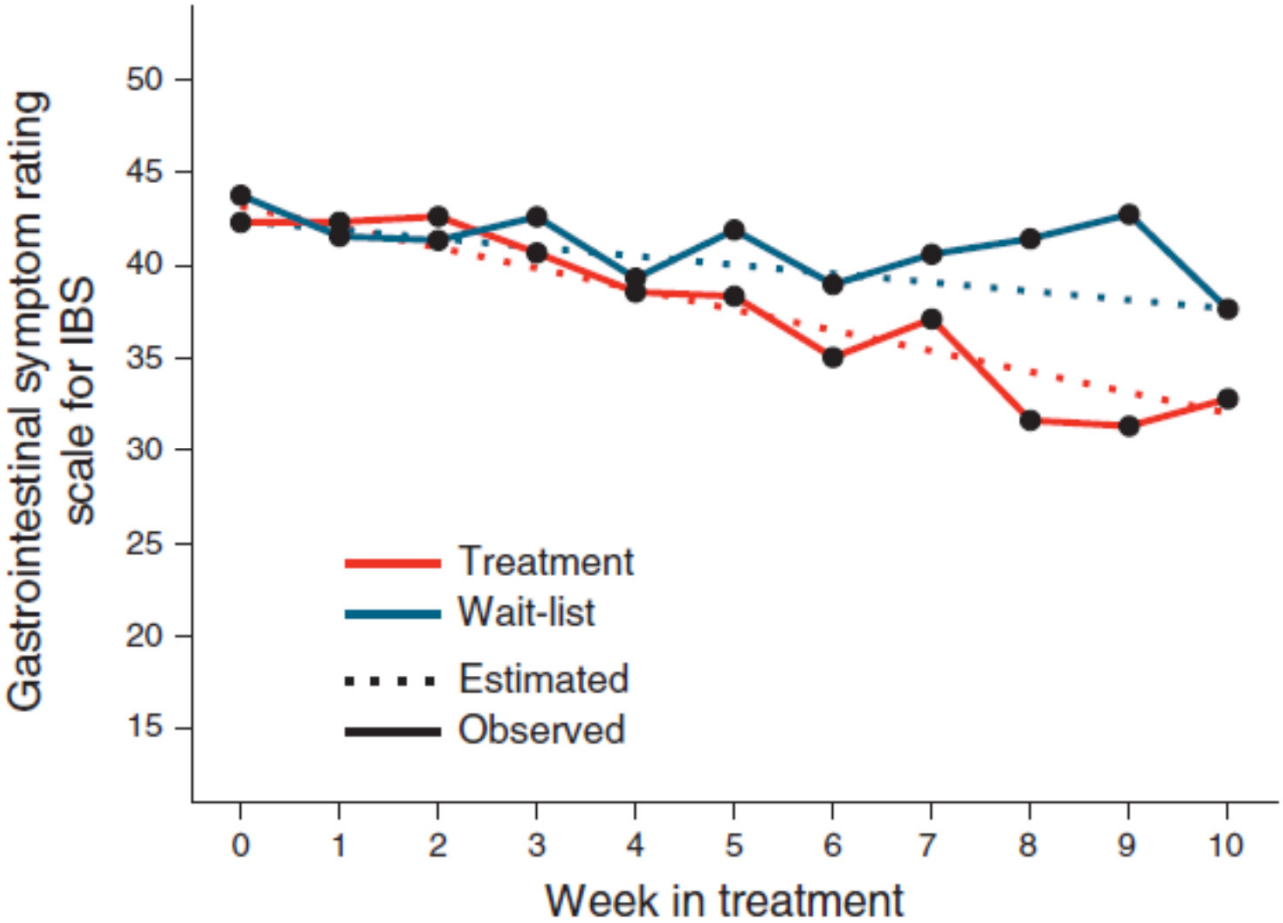
Adolescent treatment



Parent treatment



Primary outcome gastrointestinal symptoms



Bonnert M, et al. Am J Gastroenterol 2016

Hypnotherapy

- **Hypnotherapy (HT):**

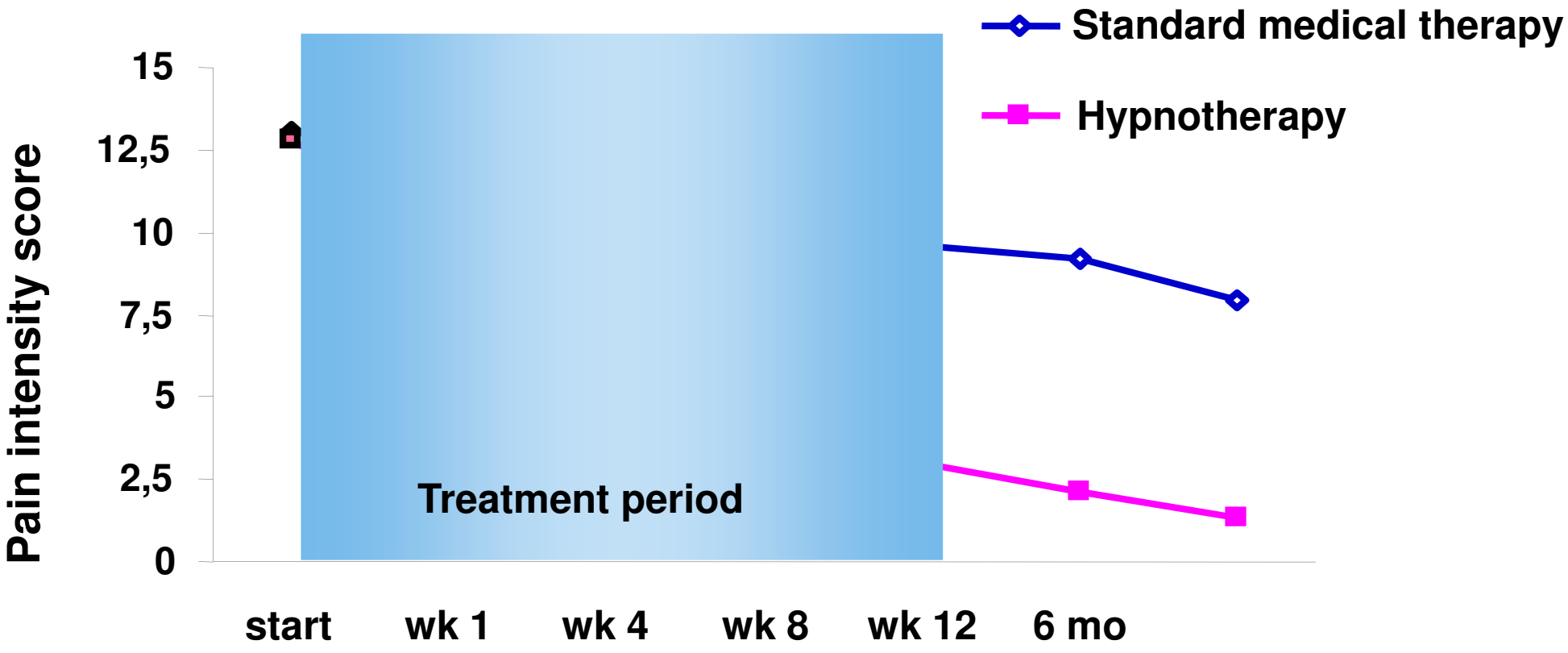
  Six sessions according to Manchester protocol

  - **general relaxation (e.g. breathing exercises)**
  - **control of abdominal pain and gut functioning**
  - **ego strengthening suggestions**

  Child is in control!

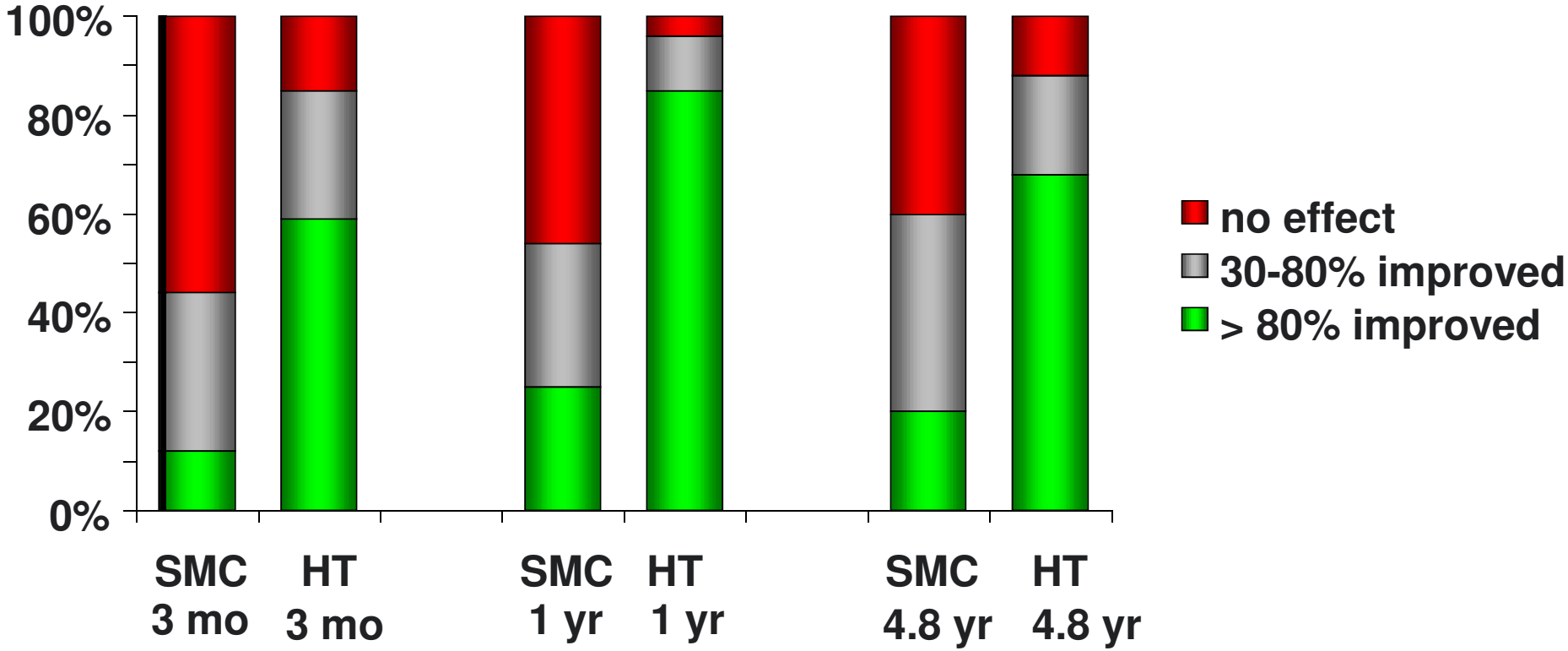
Gonsalkorale WM, et al. Int J Exp Hypn 2006

Effect of therapy on pain intensity scores



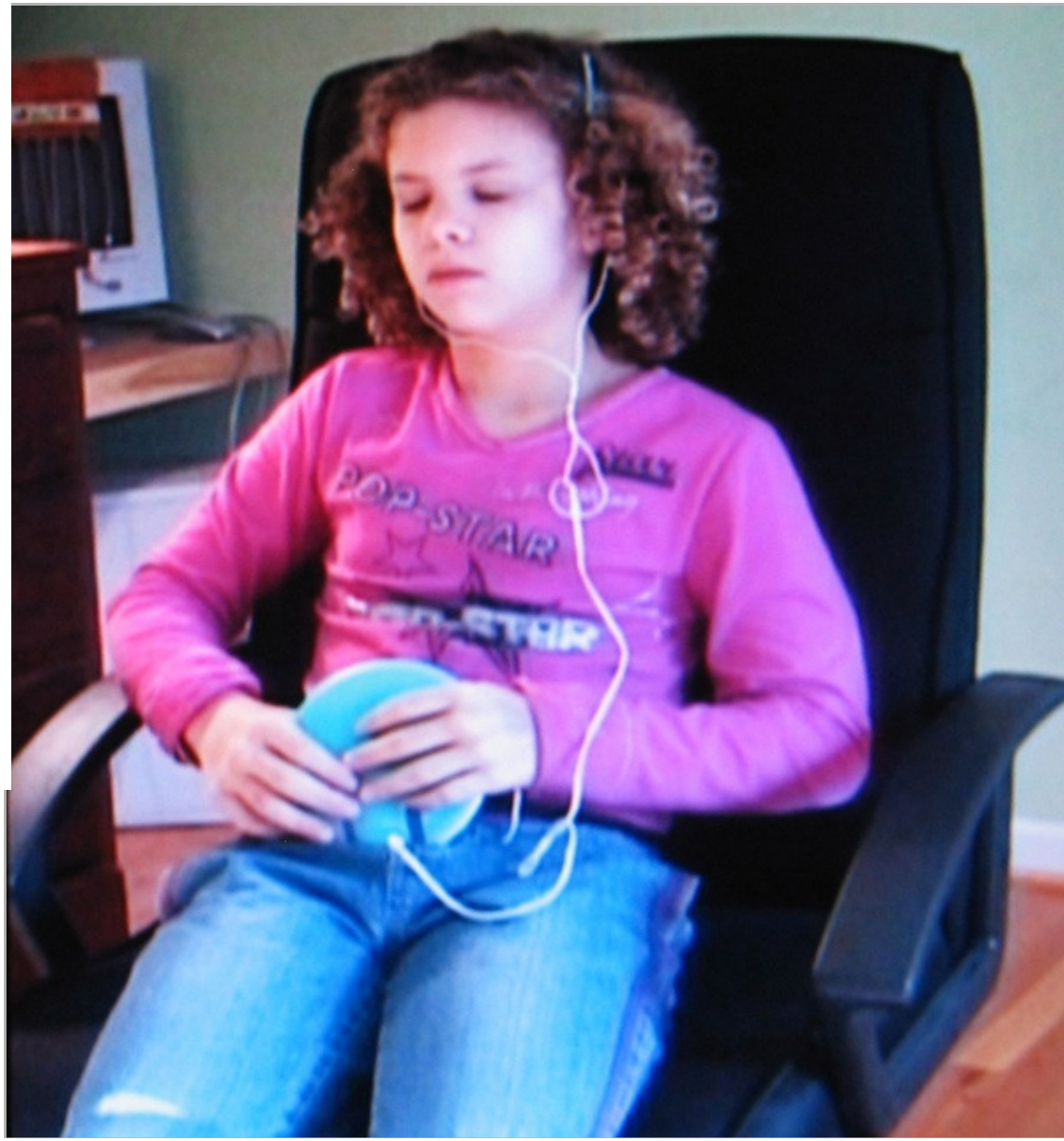
Vlieger A, et al. Gastroenterology 2006

Results – Clinical remission

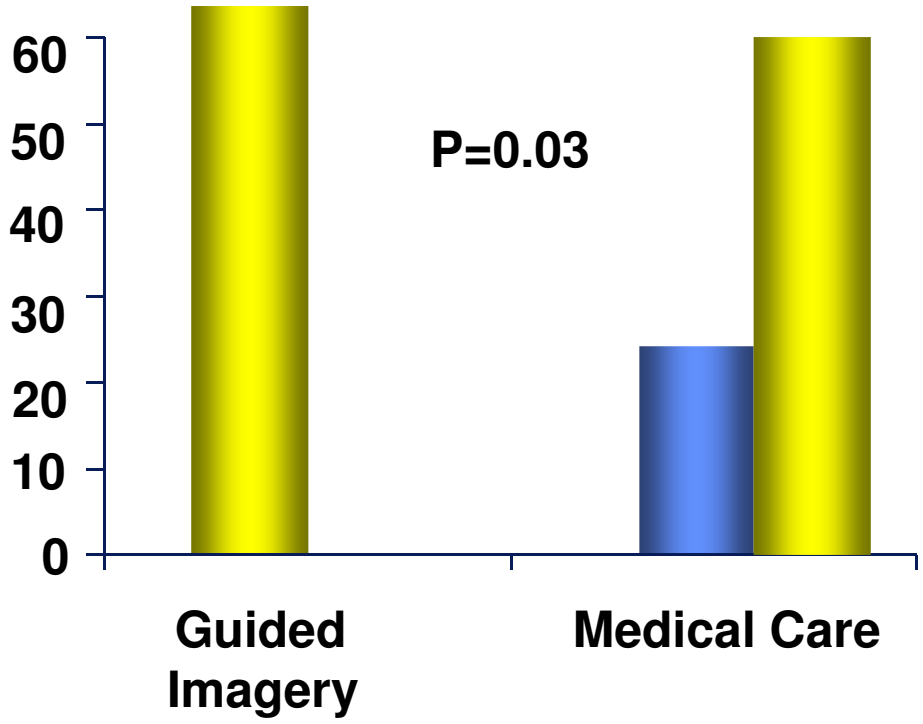


Vlieger A, et al. Am J Gastroenterol 2012

Audio-recorded Guided Imagery



Success



Van Tilburg M, et al. Pediatrics 2009

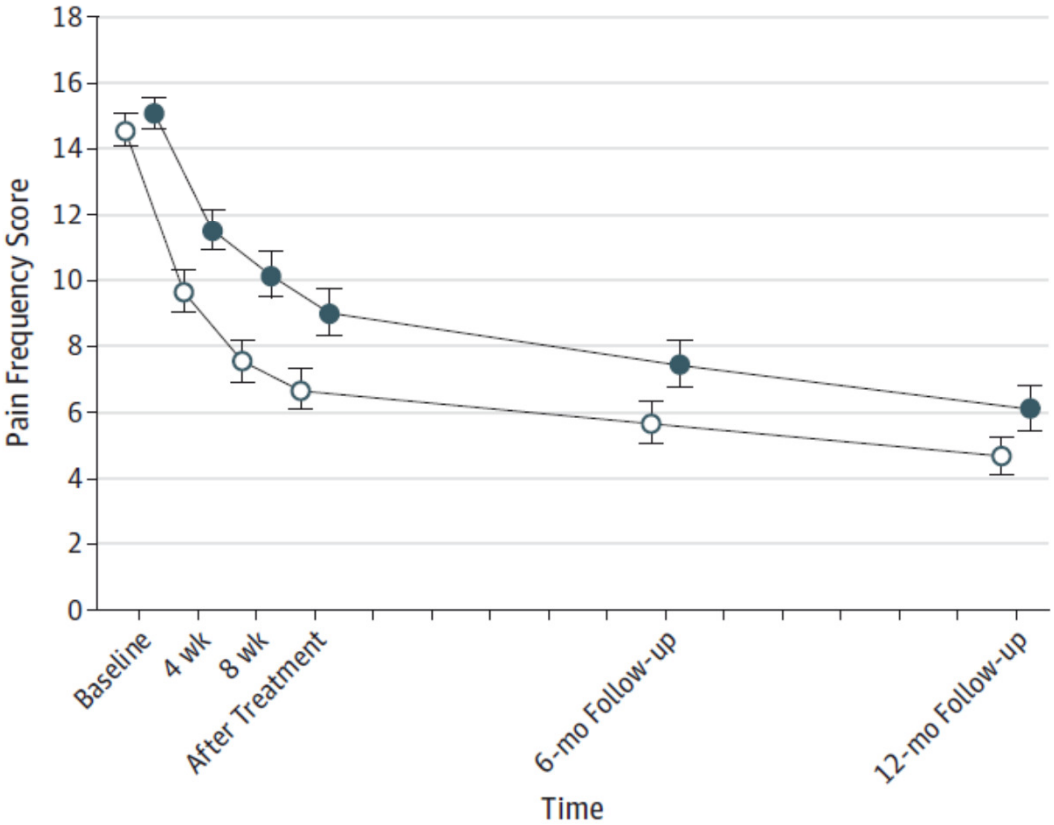
Baseline characteristics

Characteristic	CD Group (n = 126)	iHT Group (n = 124)
Age, mean (SD), y	13.4 (2.9)	13.3 (2.8)
Female	94 (74.6)	85 (68.5)
IBS		
IBS-C	39 (60.0)	35 (57.4)
IBS-D	10 (15.4)	3 (4.9)
IBS-M	14 (21.5)	20 (32.8)
IBS-U	2 (3.1)	3 (4.9)
Total IBS	65 (51.6)	61 (49.2)
FAP(S)		
FAP	22 (36.1)	29 (46.0)
FAPS	39 (63.9)	34 (54.0)
Total FAP(S)	61 (48.4)	63 (50.8)
Duration of symptoms, median (IQR), y	2.3 (1.2-5.1)	2.7 (1.1-5.3)
School absenteeism	86 (68.3)	100 (80.6)
No. of school days missed in prior 6 mo, median (IQR)	14.0 (5.0-30.0)	21.1 (4.0-24.5)
Positive family history of abdominal pain	60 (47.6)	56 (45.2)
Prior psychological treatment	19 (15.2)	24 (19.4)

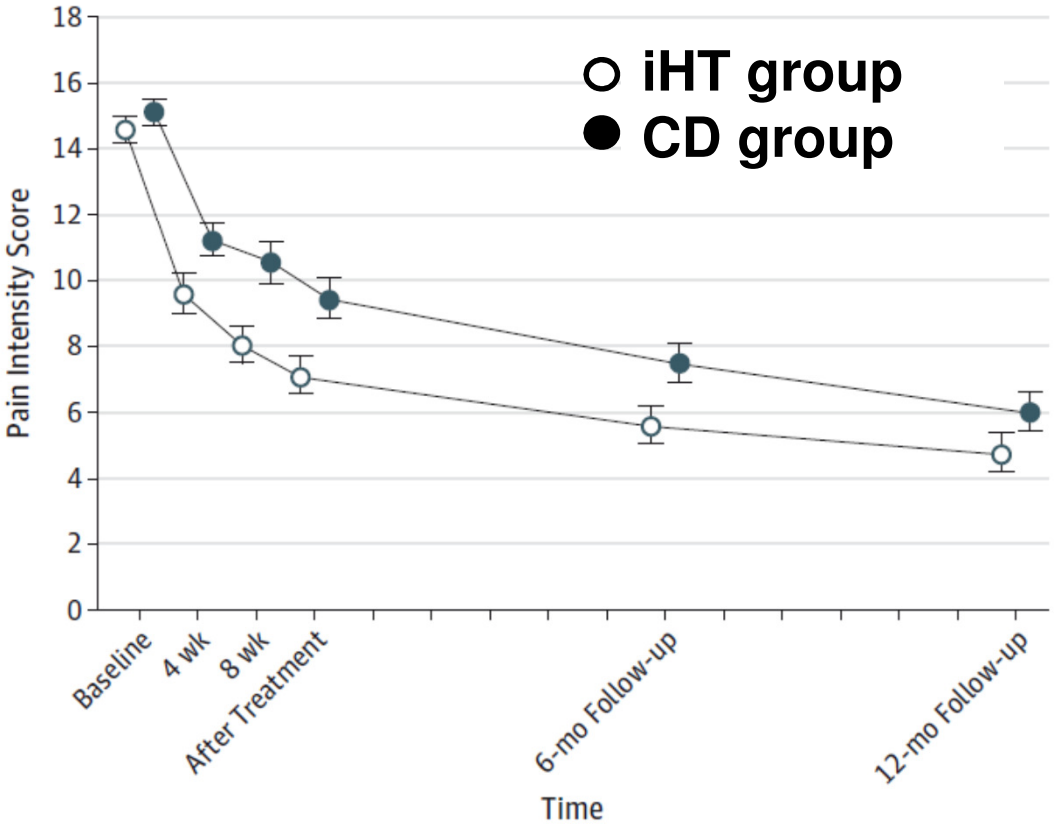
Rutten J, et al. Jama Pediatr 2017

Pain frequency and intensity scores during treatment and follow up

Pain frequency score

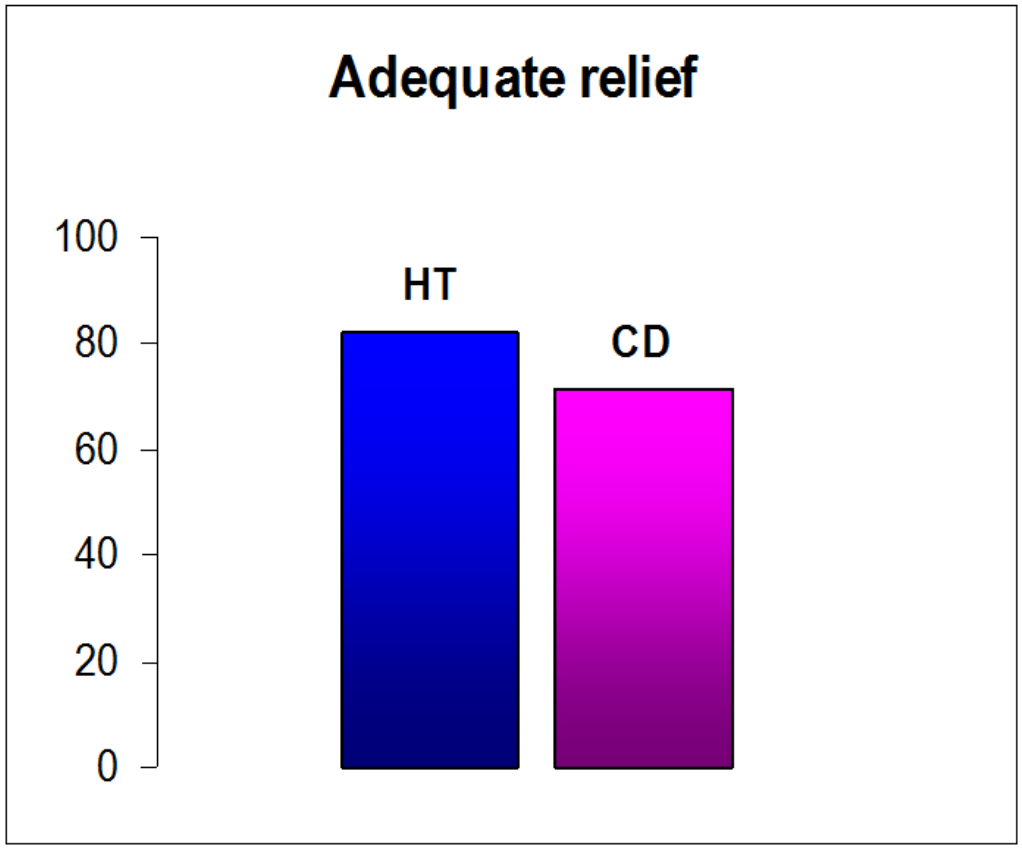


Pain intensity score



Rutten J, et al. Jama Pediatr 2017

RESULTS

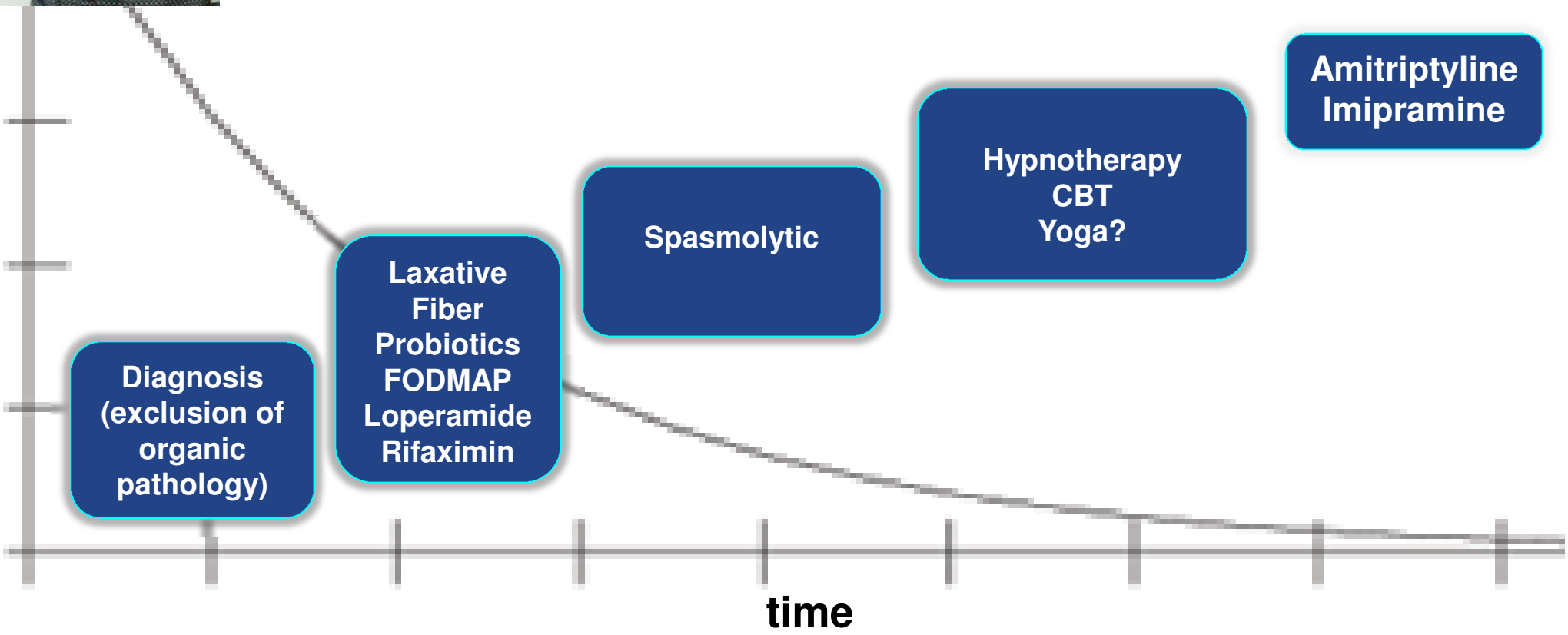


- 82.1% vs. 71.3% (p=0.07)

Rutten J, et al. Jama Pediatr 2017

Functional abdominal pain disorders; my approach

Subtypes!



The Placebo Response in Pediatric Abdominal Pain-Related Functional Gastrointestinal Disorders: A Systematic Review and Meta-Analysis

Daniël R. Hoekman, MD[1,*], Judith Zeevenhooven, BSc[1,*], Faridi S. van Etten-Jamaludin, BSc[2], luke Douwes Dekker, MD[3], Marc A. Benninga, MD, PhD[1], Merit M. Tabbers, MD, PhD[1], and Arine M. Vlieger, MD, PhD[4]

Objective To investigate the magnitude and determinants of the placebo response in studies with pediatric abdominal pain-related functional gastrointestinal disorders.

Study design The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and CINAHL were searched for systematic reviews and randomized placebo-controlled trials concerning children 4-18 years of age with an abdominal pain-related functional gastrointestinal disorder. The primary outcome was the pooled proportion of subjects assigned to placebo with improvement as defined by the authors. The effect of trial characteristics on the magnitude of the placebo response was investigated using univariate meta-regression analysis.

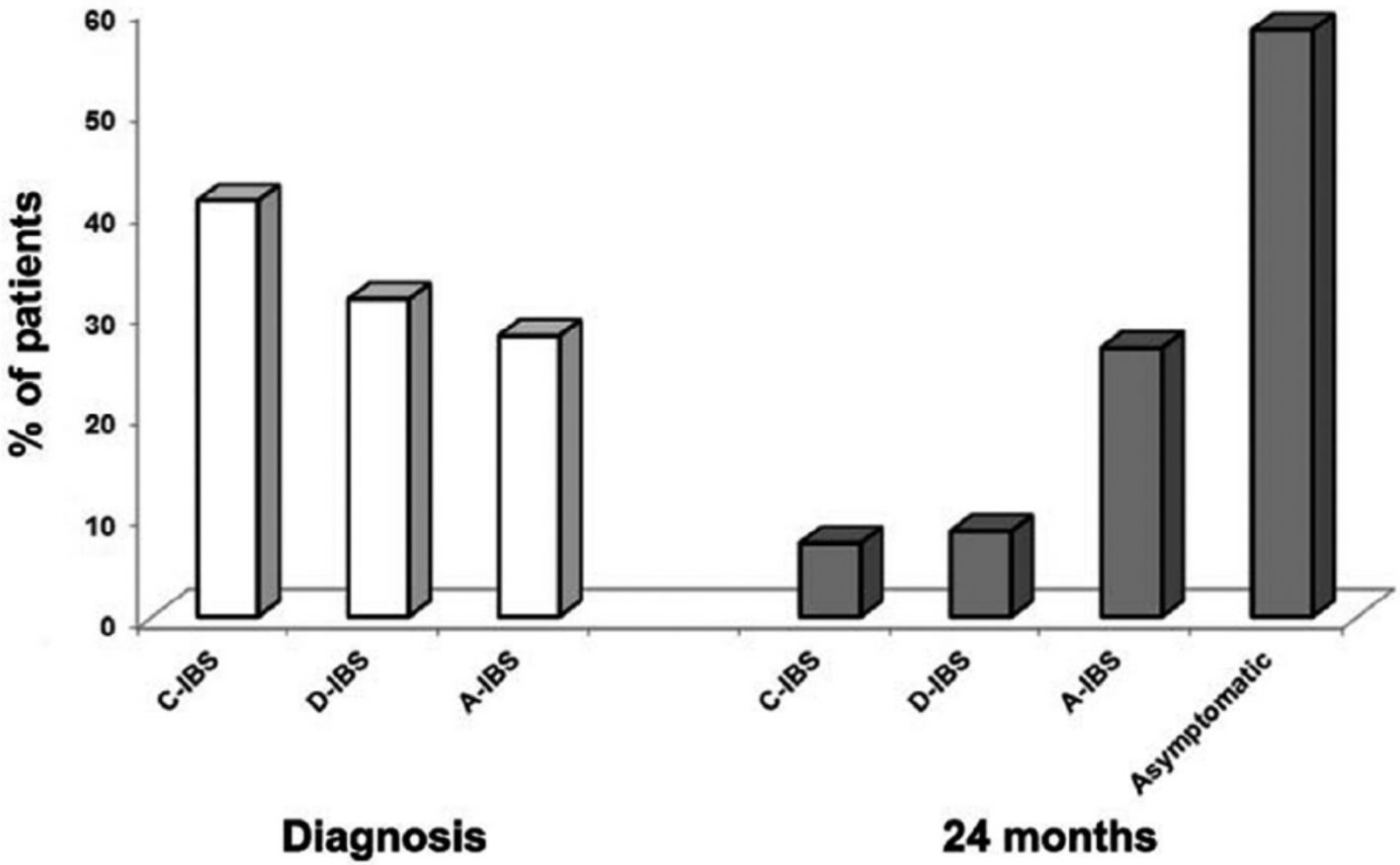
Results Twenty-one trials were identified. The pooled proportion of subjects with improvement was 41% (95% CI, 34%-49%; 17 studies) and with no pain was 17% (95% CI, 8%-32%; 7 studies). The pooled standardized mean difference on the Faces Pain Scales compared with baseline was –0.73 (95% CI, –1.04 to –0.42; 8 studies). There was significant heterogeneity across studies with respect to both outcomes. Lower dosing frequency ($P = .04$), positive study ($P = .03$), longer duration of treatment ($P < .001$), and higher placebo dropout ($P < .001$) were associated with higher [illegible] on Faces Pain Scales was greater in studies conducted in the Middle East ($P = .002$) [illegible] the randomization schedule ($P = .02$), and in studies with a higher percentage of f[illegible]

Conclusions [illegible] with abdominal pain-related functional gastrointestinal disorders improve

41%!!!

Hoekman DR, et al. J Pediatr 2017

Do children just grow out of IBS?



- Spontaneous resolution over 2 years FU
- Treatment with….. not associated with treatment success

Giannetti E, et al. J Pediatr 2017

Conclusion

- Successful management of patients with functional pain disorders with a trusting, positive, patient-physician relationship
- Fibers and probiotics only play a minor role
- The role of the FODMAP diet should be established in future larger trials
- Cognitive behavior therapy and hypnotherapy are effective treatment strategies
- Placebo??