32nd Annual Colin J. Condron, MD Care of the Sick Child Conference

TREATMENT OF ABDOMINAL PAIN DISORDERS

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Nationwide Children's Hospital

Disclosures

Scientific Consultant

- **QOL Medical**
- **Forest**
- **Quintiles**

- **Rome Criteria III**

Rasquin A, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, Walker LS. Gastroenterology. 2006;130:1527-374.

- **Rome Criteria IV- 2015**

  - Carlo Di Lorenzo – Chair
  - Jeffrey Hyams – Co-Chair
  - Miguel Saps
  - Robert Shulman
  - Annamaria Stajano
  - Miranda Van Tilburg

Abdominal pain–related FGIDs

- Functional dyspepsia
- Irritable bowel syndrome
- Abdominal migraine
- Childhood functional abdominal pain (syndrome)

- At least once/week for at least 2 months before diagnosis

Functional Dyspepsia

- **Persistent/recurrent pain or discomfort (uncomfortable sensation not described as pain) in upper abdomen**

- **Not relieved by defecation or associated onset of change in stool frequency/form**

Irritable Bowel Syndrome

- **Abdominal discomfort/pain associated with 2 or more of the following at least 25% time:**

- **Improved with defecation**
- **Onset associated with a change in stool frequency or form**

Functional Abdominal Pain

- Episodic or continuous abdominal pain
- Insufficient criteria for other FGIDs

- Syndrome- At least 25% of time 1 or more:
- Loss of daily functioning
- Additional somatic symptoms such as headache, limb pain, or difficulty sleeping

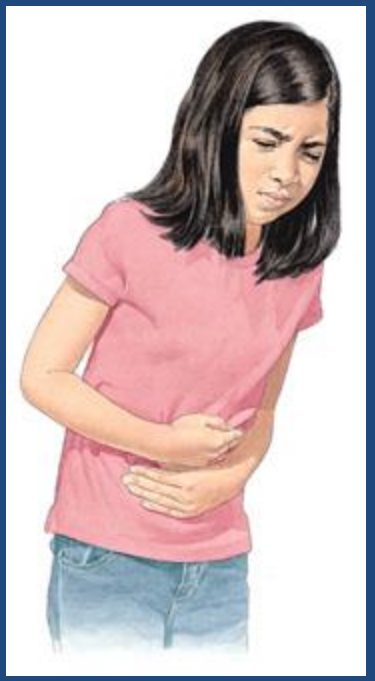
Abdominal Migraine

- Paroxysmal episodes of intense, acute periumbilical pain that lasts for 1 hour or more

- Intervening periods of usual health lasting weeks to months

- Pain interferes with normal activities

- Pain is associated with 2 or more of:
- *Anorexia*
- Nausea
- Vomiting
- *Headache*
- Photophobia
- *Pallor*

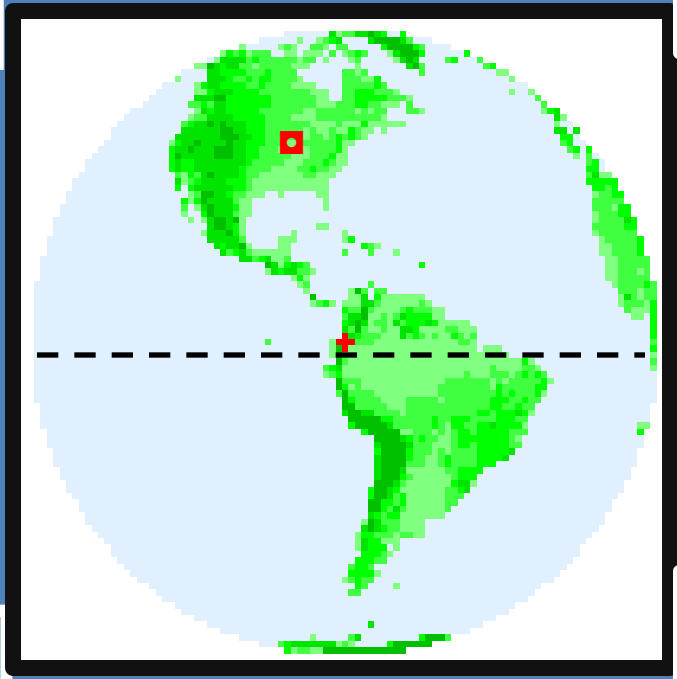


Abdominal Pain

- 4 Weeks 52%
- 8 weeks 24%
- 12 weeks 18%

Saps M, et al. J Pediatr. 2009;154:322-6.


PROMOCIONES
EL MANICOMIO
PRECIOS DE LOCURA
disco
riedades




McDonald's

Weekly Prevalence of Symptoms USA vs. Colombia

	Colombia n=265	USA (historical data) n=237	Significance
Gastrointestinal Symptoms	Saps M, et al. NASPGHAN 2011	Saps M, et al. J Pediatr. 2009;154:322-6.	
Abdominal Pain	35%	38%	NS
Nausea	25%	23%	NS
Constipation	11%	8%	NS
Diarrhea	8%	9%	NS
Vomiting	7%	7%	NS
Non- Gastrointestinal Symptoms			
Headaches	31%	42%	<0.01
Pains Arms Legs	39%	36%	NS
Chest Pain	25%	15%	0.02

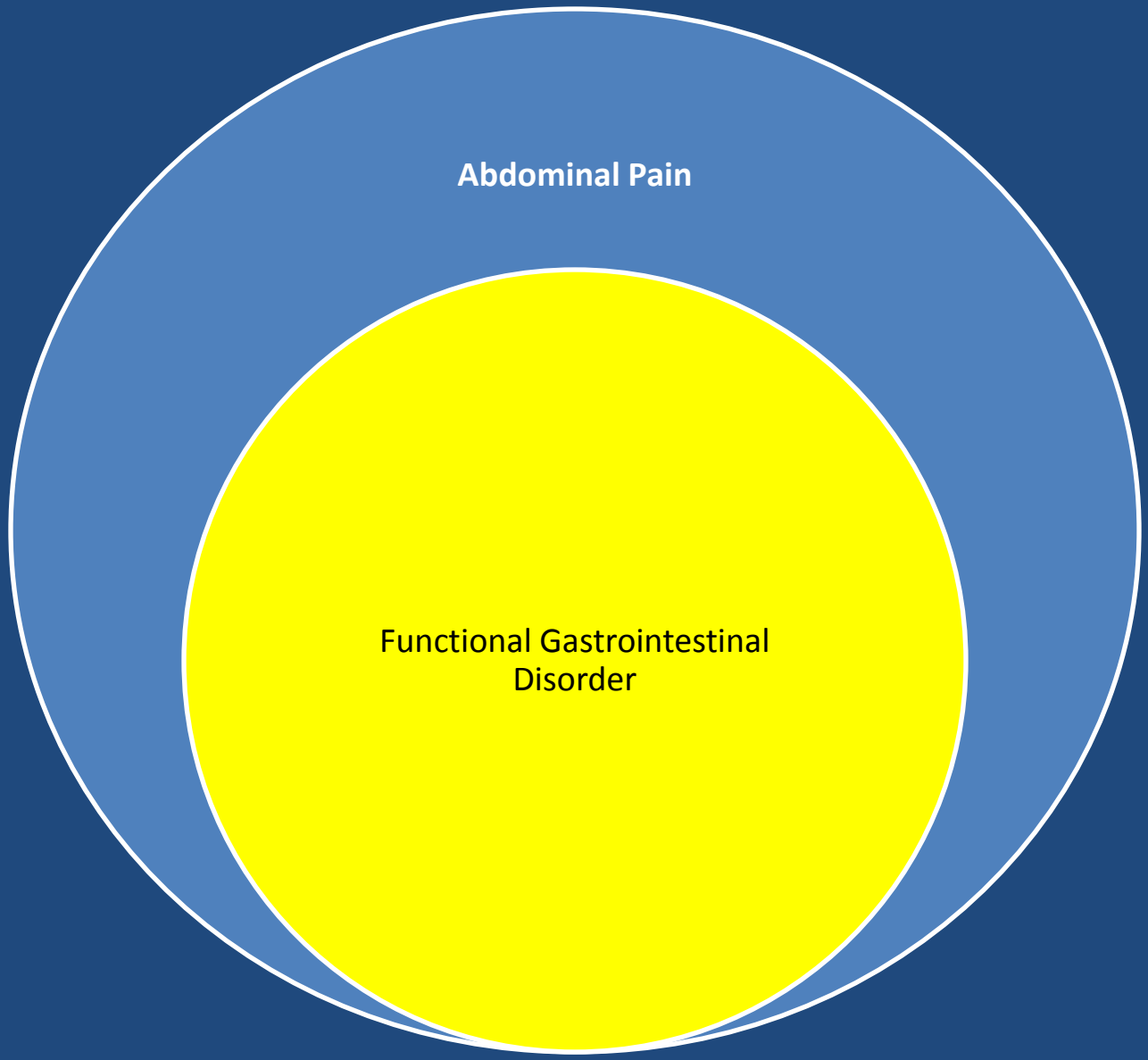
Abdominal Pain Interference	
Any activity	56%
Gym	19%
School	14%
Sleep	12%
Social	11%

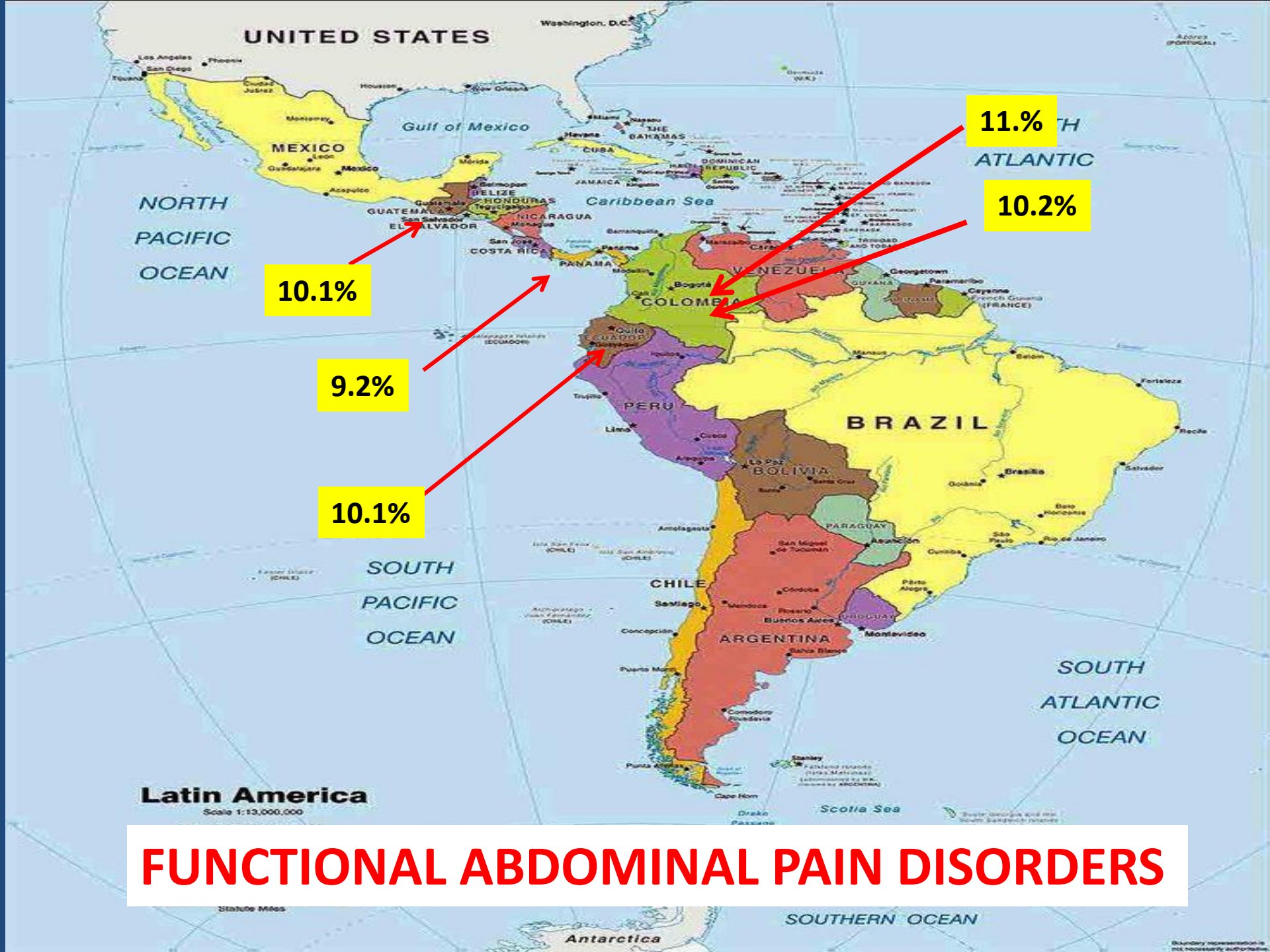
Saps M, et al. J Pediatr Gastroenterol Nutr 2011;53 (Suppl 1), E66.

23% missed school (mean 2.3 days)

10% parents miss work (mean 1.9 days)

Saps M. et al. J Pediatr. 2009;154:322-6


Abdominal Pain
Functional Gastrointestinal Disorder



FUNCTIONAL ABDOMINAL PAIN DISORDERS

Prevalence
Functional Gastrointestinal Disorders (%)

	Participants 4635	FGIDs	Pain Disorders	IBS	
Colombia 1	373	29	11.1	5.4	Saps et al. J Pediatr. 2014
Colombia 2	3198	27.3	10.2	5.4	
Ecuador	417	22.8	10.1	4.8	Koppen IJ, Saps et al. Under review
Panama	321	28.7	12.2	5.6	Lu P, Saps et al. Under review
El Salvador	399	20.3	9.2	3.8	Zablah, Bonilla S, Saps et al. Rev Gastroenterol Mex. 2015
Sri-Lanka	427		13.8	7	Devanarayana NM, et al. J Trop Pediatr. 2011
Nigeria	874		9.9	5.6	Udoh E, et al. J Pediatr Gastroenterol Nutr. 2015
USA	507			6	Hyams JS, et al.

Psychosocial stressors

Pain episode

Infection / inflammation

Appraisal of Pain Episode

Risk factors: Genetics, Gender, Early life events

Protective factors: Culture, Gender Social support

Coping with Pain Episode

Episode Outcome

Maladaptive response

Chronic Pain

Accommodation

Normal development

Potential Long-term Outcomes

Health-Related Quality of Life

	AP-FGIDs Rome III	Controls	FAP Rome II	Controls
	Sri-Lanka		USA	
Physical	84	91	82	86
Social	85	93	86	88
Emotional	74	83	76	81
School	75	82	74	81
Overall scores	80	88 *	80	86
	Devanarayana NM et al. BMC Gastroenterol. 2014 21;14:150		Varni et al. J Dev Behav Pediatr. 2006 ;27:451-8	

*p < 0.001

Health-related quality of life (HRQOL)

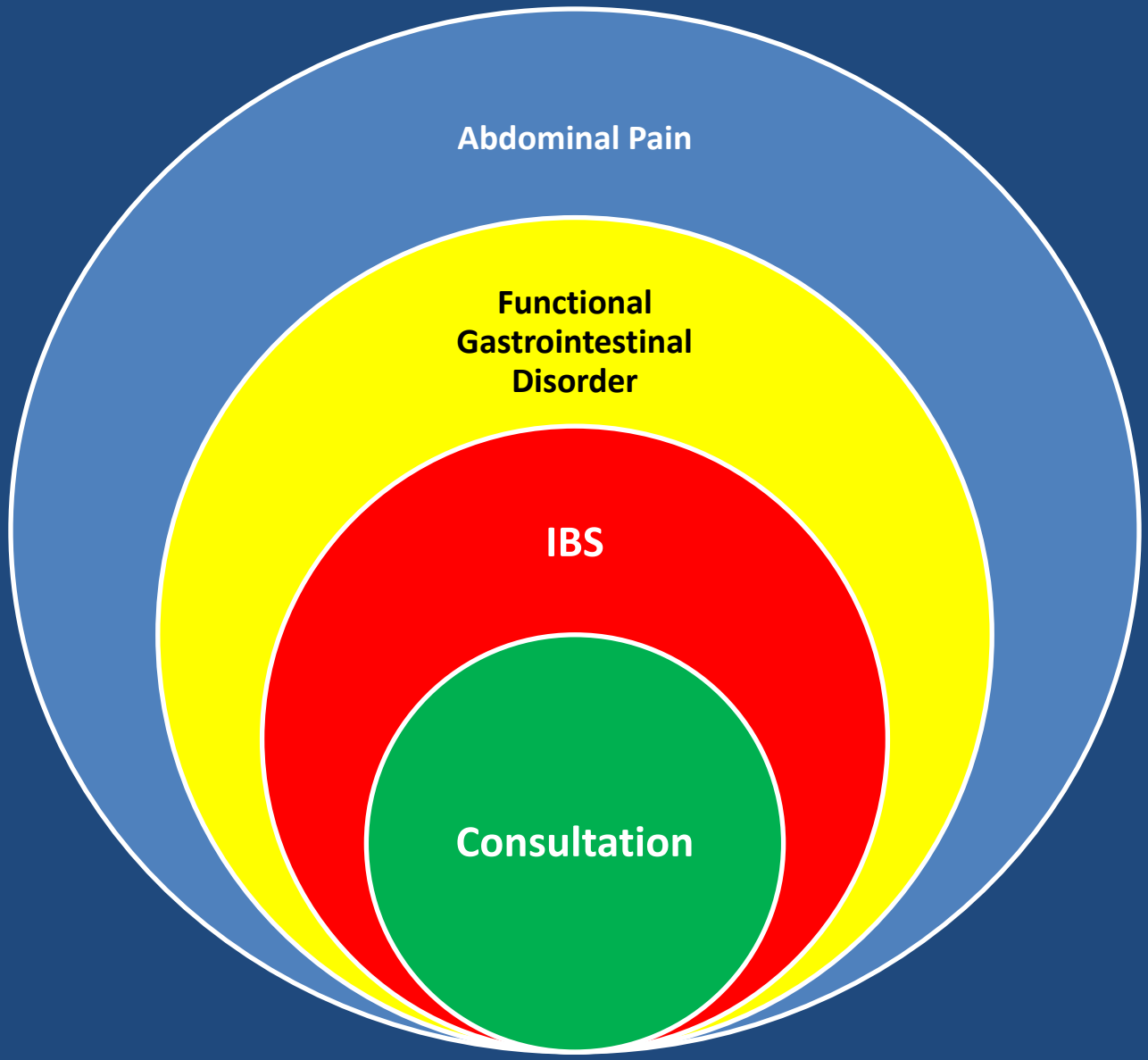
Varni, et al. J Pediatr. 2015;166:85-90.

FGIDs and IBD vs. Healthy Controls

- Both lower HRQOL than healthy controls
- Physical
- Emotional
- Social
- School

FGID vs. IBD

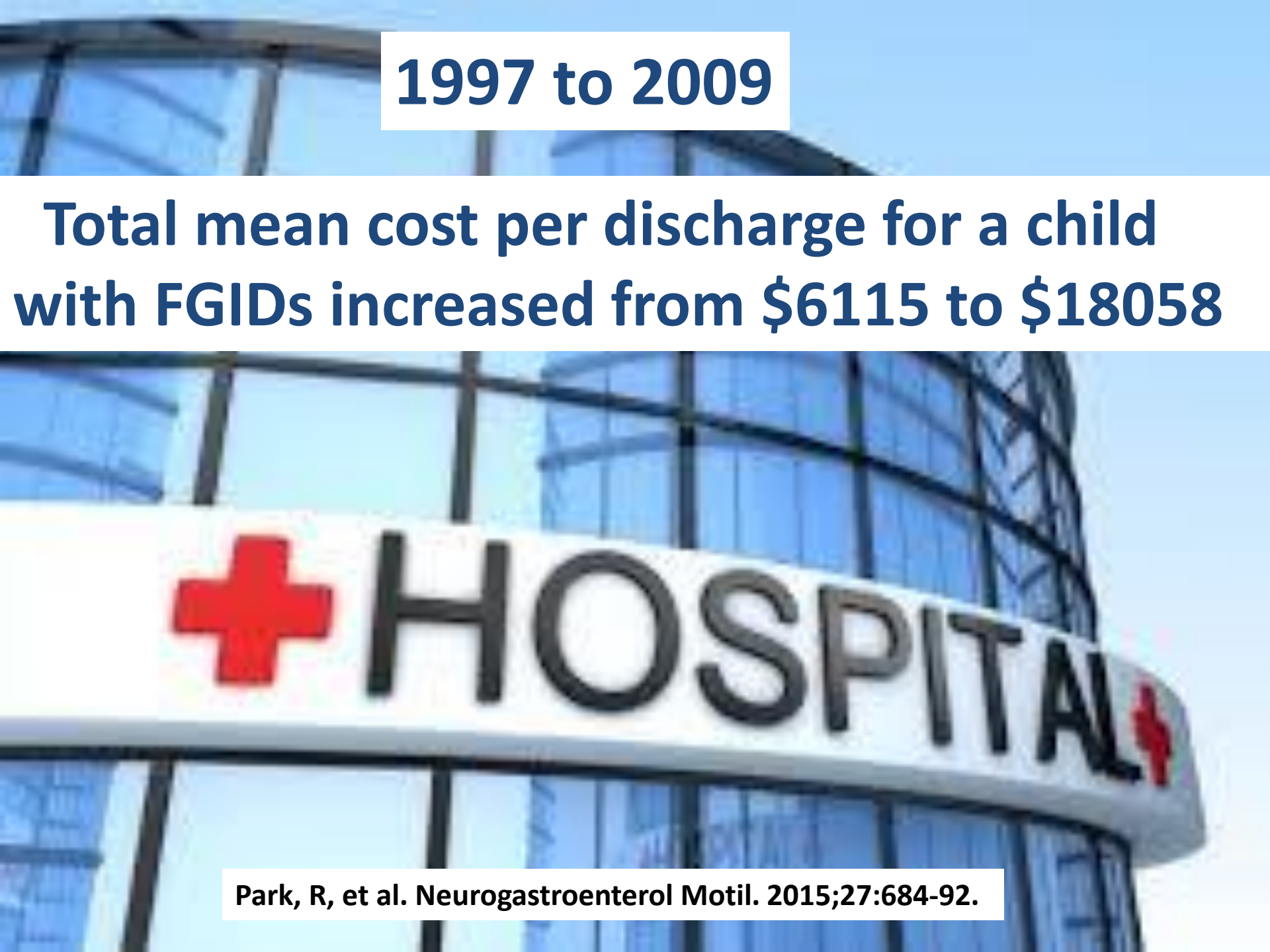
- FGID Lower HRQOL than IBD
- Missed more school
- Spent more days in bed
- Greater healthcare utilization
- Parents missed more work


Abdominal Pain
Functional
Gastrointestinal
Disorder
IBS
Consultation

Saps M. et al. J Pediatr. 2009;154:322-6
Saps M, et al. J Pediatr. 2014;164:542-5

Abdominal Pain

2-4 % seek medical attention for abdominal pain



1997 to 2009

Total mean cost per discharge for a child with FGIDs increased from $6115 to $18058

Park, R, et al. Neurogastroenterol Motil. 2015;27:684-92.

A Million Dollar Workup for Abdominal Pain. Is It Worth It?

Dhroove G, Chogle A, Saps M. J Pediatr Gastroenterol Nutr. 2010;51:579-83

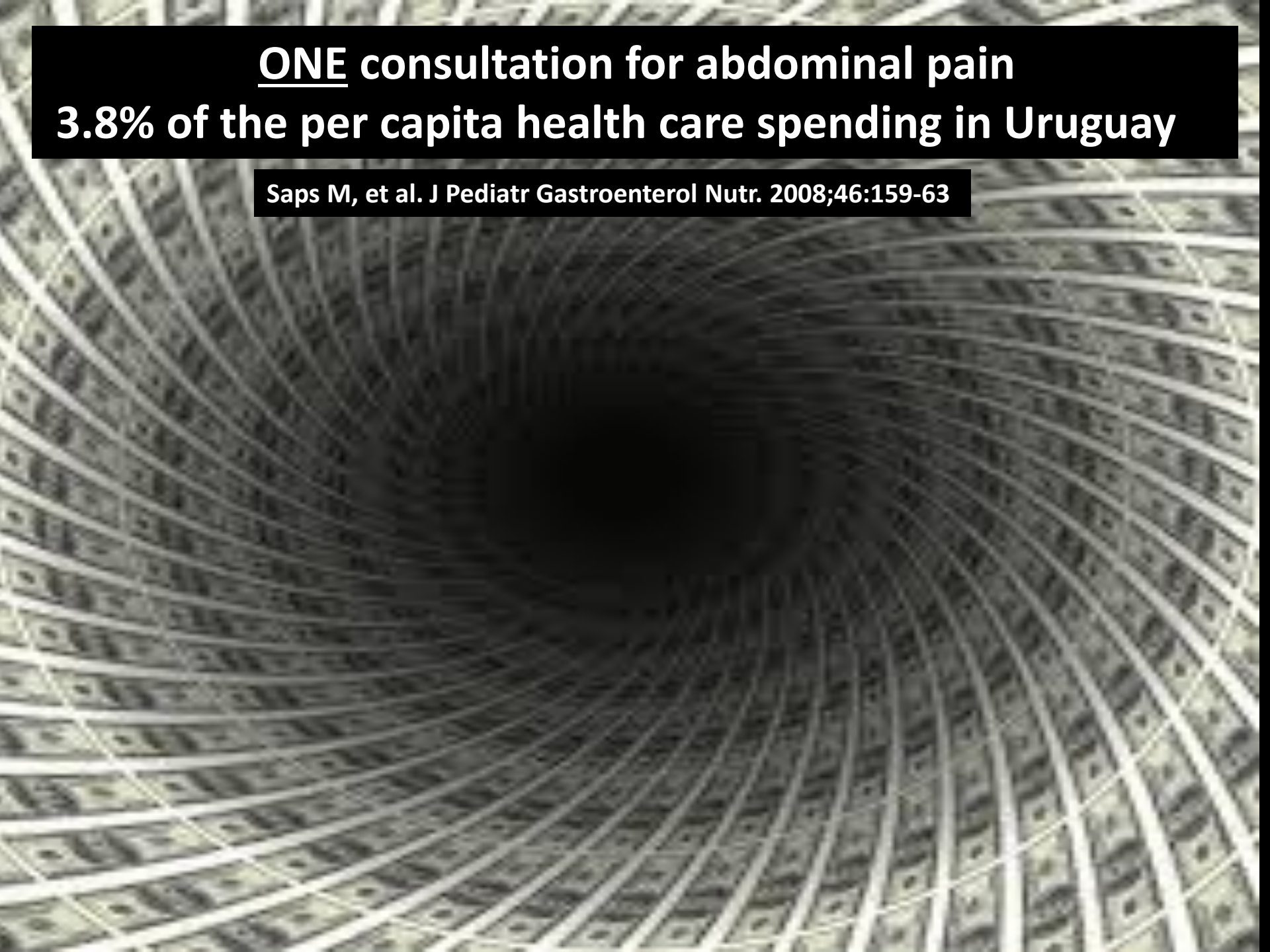
34% esophagogastroduodenoscopy 10% abnormal: H. pylori, chemical gastritis, esophagitis 17%, colonoscopy 9.5% abnormal: rare fork crypts, lymphoid hyperplasia

Average cost per patient: $6104.

Total annual costs/patient €2512

- **Inpatient (22.5%)**
- **Outpatient (35.2%)**
- **Parents productivity loss 22% of total costs**

Hoekman DR J Pediatr. 2015

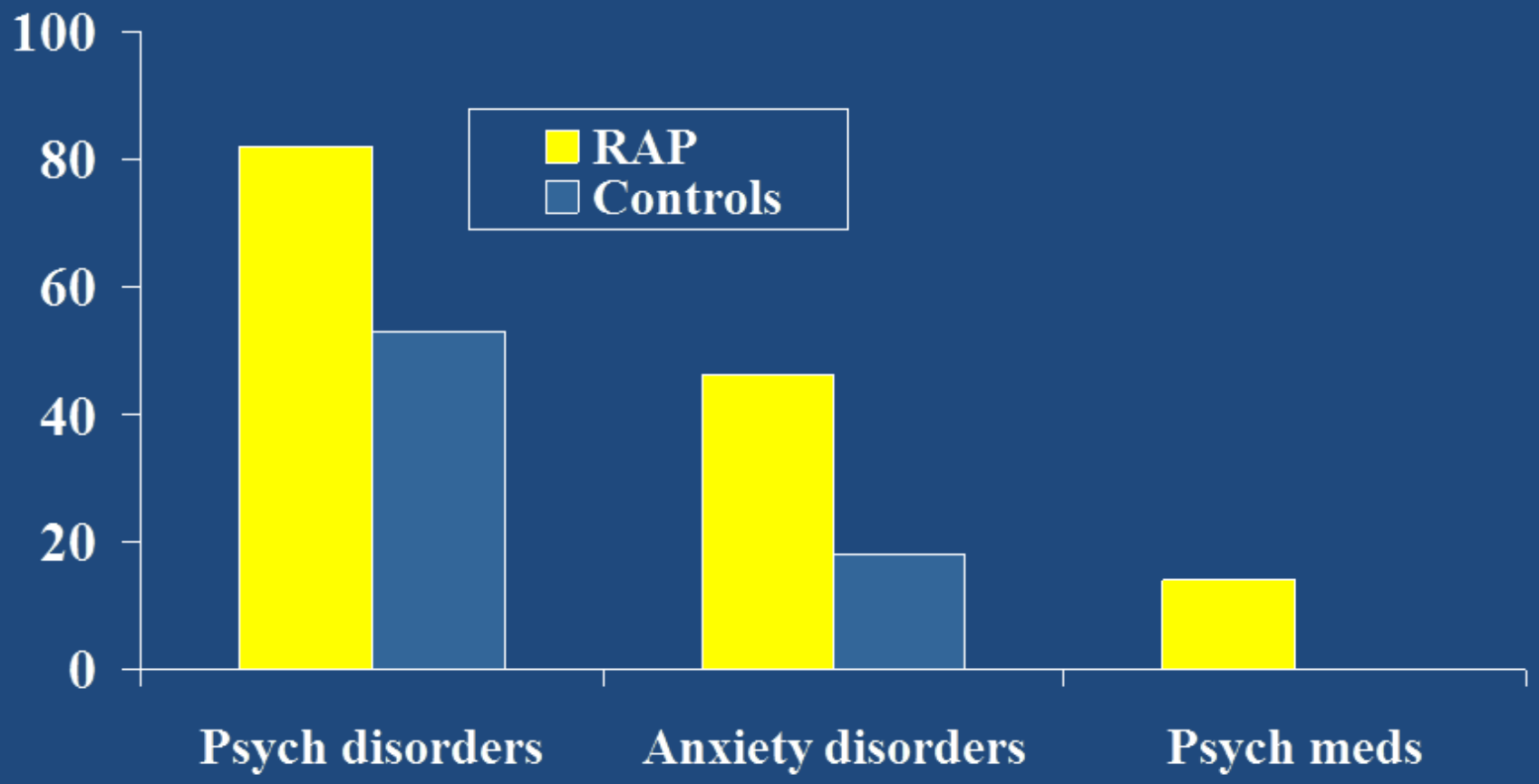

ONE consultation for abdominal pain
3.8% of the per capita health care spending in Uruguay
Saps M, et al. J Pediatr Gastroenterol Nutr. 2008;46:159-63

Comorbidities

Campo JV et al. Pediatrics. 2004 ;113:817-24

- FAP patients in primary care more likely to be diagnosed with a psychiatric disorder
- Higher levels of anxiety and depressive symptoms, functional impairment than controls.
- Anxiety disorder in 79%
- Depressive disorder in 43%

Adult outcomes of FAP



Campo JV et al. Pediatrics 2001; 108: E1


dreamstime.com


Drugs

American Academy Pediatrics y North American Society of Pedatric Gastroenterology Hepatology and Nutrition y Cochrane Systematic Review: "Little evidence pharmacological treatments"

Di Lorenzo C. et al. J Pediatr Gastroenterol Nutr. 2005;40:249-61.

Huertas-Ceballos A, et al. Cochrane Database Syst Rev. 2008;CD003017.

Challenges of caring for children with functional gastrointestinal disorders.

Saps M. Pediatr Ann. 2014;43:141-2.

NO DRUGS approved by FDA for the treatment of IBS in children!!!

The use of non-narcotic pain medication in pediatric gastroenterology

Miranda A, Saps M. Paediatr Drugs. 2014;16:293-307

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Antispasmodics

Ford AC, et al. BMJ. 2008

NO DATA IN CHILDREN

- **Systematic review and meta-analysis of randomized controlled trials**

- **12 different antispasmodics with placebo in 1778 patients: otilonium, cimetropium, hyoscine, pinaverium, trimebutine, trimebutine and rociverine, alverine, dicycloverine (dicyclomine), mebeverine, pirenzipine, prifinium, propinox.**
- **NONE USA**

Antispasmodics

Ford AC, et al. BMJ. 2008

.

Persistent symptoms

39% drug vs. 56% placebo

RR 0.68 (95% confidence interval 0.57 to 0.81)

NNT = 5 prevent symptoms/one patient (95% CI 4-9).

Peppermint Oil

- Antispasmodic- Ca2+ blocker, interaction with sensory neurons (TRP channels)
- Multicenter (3 centers), randomized double blind
- 42 children, 8-17 years, IBS
- 2 weeks. 30-45 Kg 1 capsule enteric coated, >45 Kg- 2 capsules 187 mg or placebo 3/day
- 75% reduction in severity of pain vs. 43% placebo (79% improvement adults)
- No side effects

Kline RM, et al. J Pediatr.2001;138:125-8

Cyproheptadine

Sadeghian M. et al. Minerva Pediatr. 2008;60:1367-74.

- Randomized double blind placebo-controlled trial.
- N=29 children functional abdominal pain
- 2 weeks medication vs. placebo
- Cyproheptadine: 0.25-0.5 mg/kg/day (12 mg max) in 2-6 years and 16 mg 6-12 years
- Week 1 and 2 ⇓ intensity/ frequency pain
- Improved or resolved pain- 86% medication vs. 36% placebo

Rodriguez L, et al. J Pediatr. 2013 ;163:261-7.

Safety and efficacy of cyproheptadine for treating dyspeptic symptoms in children

Retrospective, open label study

Patients with underlying organic cause of dyspepsia, and no organic cause

Response to therapy - 55%

Cyproheptadine use in Children with Functional Gastrointestinal Disorders

Retrospective open label study

Patients who had follow-up (151/307)

Improvement

- Rome criteria 73%
- IBS 100%
- Abdominal migraine 72%
- CVS 75%

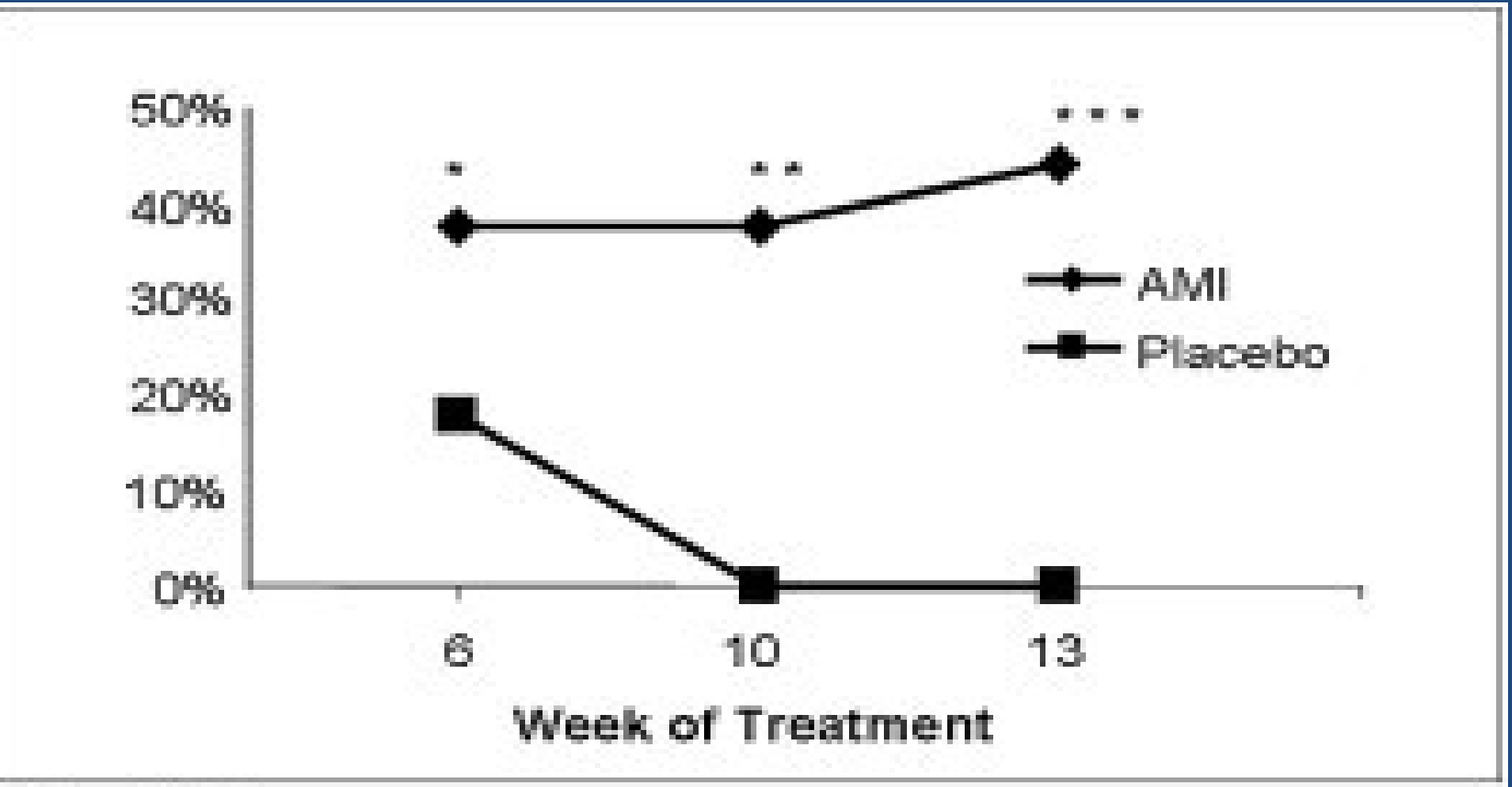
Madani S, et al. JPGN 2015

Cyproheptadine Side Effects

	Rodriguez L, et al. J Pediatr. 2013 ;163:261-7.	Madani S, et al. JPGN 2015
Side effects	30%	32%
Sleepiness	16%	12%
Increase appetite	5%	1%
Weight gain		10%
Irritability	6%	
Abdominal pain	2.5%	
Discontinuation due to side effects	2.5%	15%

Double-blind Placebo-Controlled Trial of Amitriptyline for the Treatment of Irritable Bowel Syndrome in Adolescents

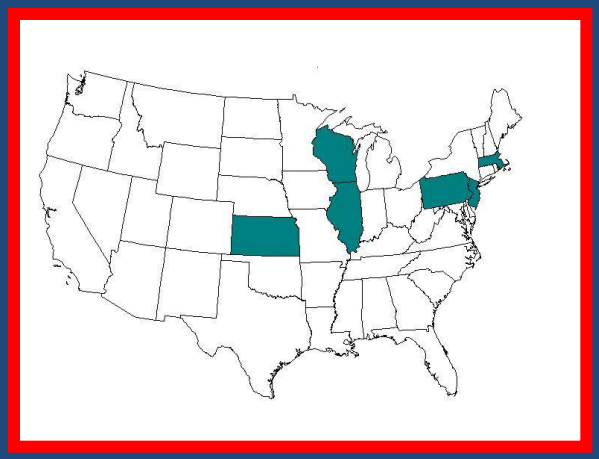
Ron J. Bahar, MD, Brynie S. Collins, MD, Barry Steinmetz, MD, and Marvin E. Ament, MD



* p = 0.26
** p = 0.007
*** p = 0.002

	IBS-associated diarrhea	Periumbilical pain	RLQ pain
Week 6			
AMI	−50 ± 12.9	−18.8 ± 10.1	−25 ± 14.4
Placebo	−11.8 ± 11.8	5.9 ± 10.4	17.6 ± 9.5
P value	.029	.089	.014
Week 10			
AMI	−50 ± 12.9	−12.5 ± 8.5	−12.5 ± 8.5
Placebo	−11.8 ± 11.8	17.6 ± 9.5	11.8 ± 8.1
P value	.029	.018	.039
Week 13			
AMI	−37.5 ± 12.5	−12.5 ± 12.5	−25 ± 11.2
Placebo	−11.8 ± 11.8	17.6 ± 9.5	17.6 ± 9.5
P value	.134	.055	.004

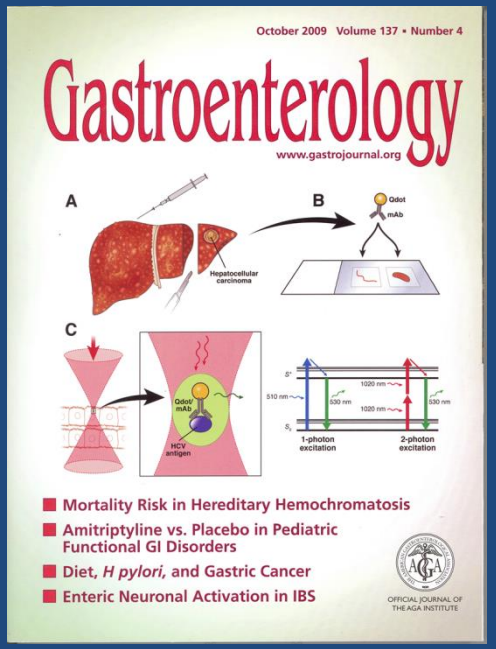
Multicenter Randomized Double-Blinded Placebo Controlled Trial



- Children's Hospital of Pittsburgh
- Morristown Memorial Hospital (NJ)
- Children’s Memorial Hospital (Chicago)
- Children’s Hospital of Boston
- Children’s Hospital of Wisconsin
- University of Kansas Medical Center

Multicenter Randomized Double-Blinded Placebo Controlled Trial

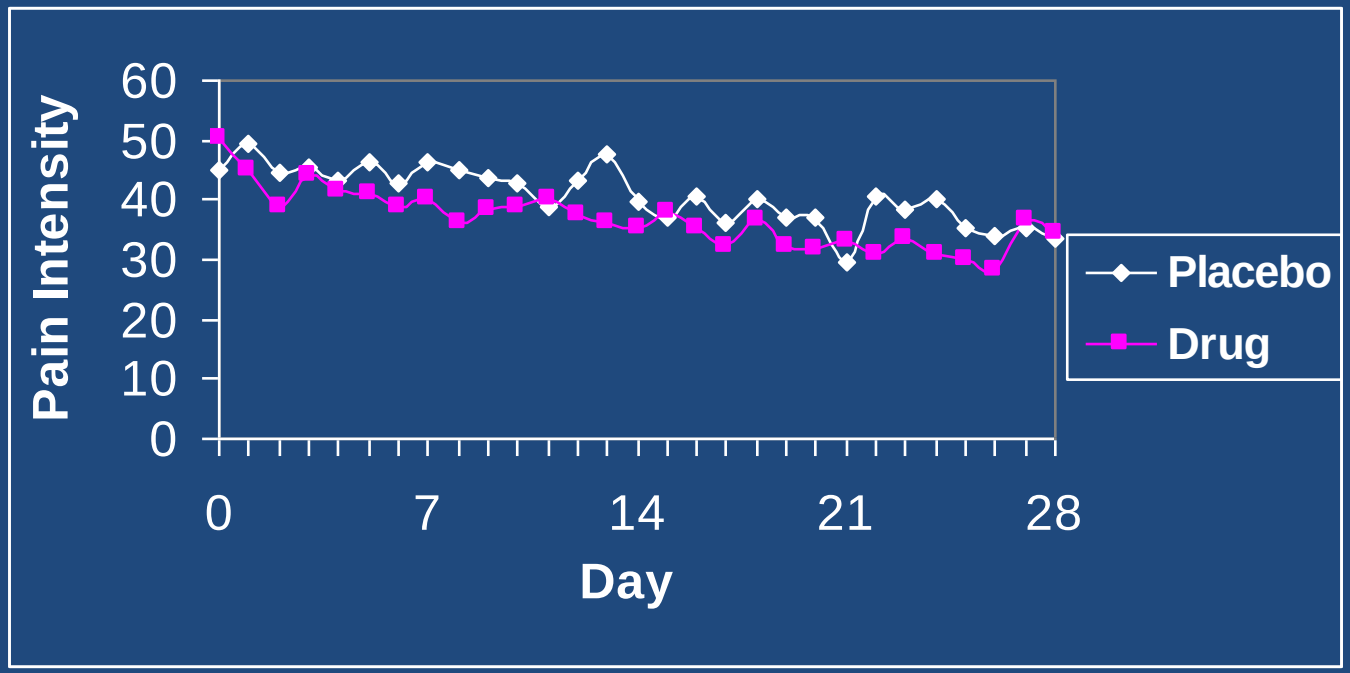
- 4 weeks
- 10 mgs < 35 kg
- 20 mgs ≥ 35 kg



	Amitriptyline	Placebo	
Better	63 %	57%	NS
Good/Excellent	53%	50%	NS

Saps M, et al. Gastroenterology. 2009.

Daily Pain Intensity



Significant improvement of pain ($p<0.0001$).
Trend difference between groups ($p=0.90$).

Intention to Treat vs. Per Protocol

Teitelbaum JE, et al. J Pediatr Gastroenterol Nutr. 2011;53:260-4.

- 146 prescribed- 98/146 received medication, followed
- Intention to Treat: 77/146 responders

79% vs. 53%

	Total	Amitriptyline		Placebo	
Failed	17%	16 %		17.5 %	
Poor	12%	16 %		7.5 %	
Mild	19 %	14%		25 %	
Good	40%	37%	**53%**	42.5 %	**50%**
Excellent	12 %	16 %		7.5 %	

Citalopram

Campo et al.

Roofhaza H, et al NGM 2014

European Review for Medical and Pharmacological Sciences 2013; 17: 1314-1320

Rifaximin treatment for small intestinal bacterial overgrowth in children with irritable bowel syndrome: a preliminary study

E. SCARPELLINI, V. GIORGIO*, M. GABRIELLI, S. FILONI*, G. VITALE, A. TORTORA, V. OJETTI, G. GIGANTE, C. FUNDARÒ*, A. GASBARRINI

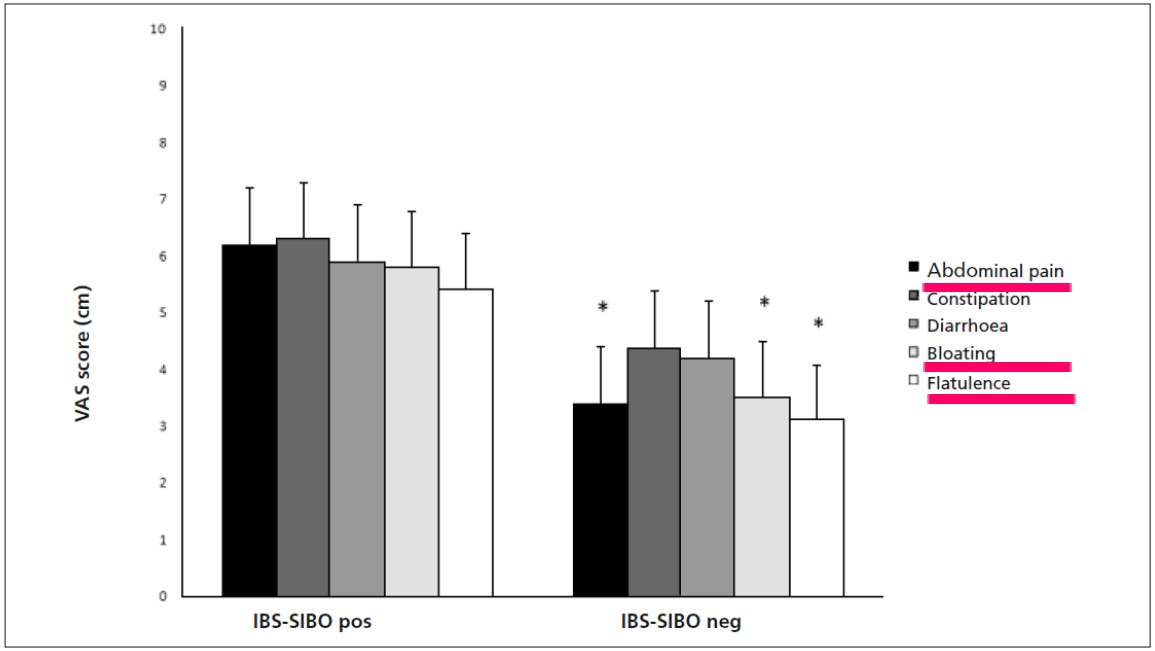


Figure 2. VAS score in IBS children after rifaximin treatment.

Rifaximin 600 mg/day effective and safe for the treatment of bacterial overgrowth and irritable bowel syndrome in children

ORIGINAL ARTICLE: GASTROENTEROLOGY

Double-blind, Placebo-controlled Antibiotic Treatment Study of Small Intestinal Bacterial Overgrowth in Children With Chronic Abdominal Pain

*Brynie Slome Collins and †Henry C. Lin

J Pediatr Gastroenterol Nutr. 2011;52:382-6.

- 75 children- 50 drug vs. 25 placebo
- 600 mg rifaximin/8 hours for 10 days
- NS in any symptom

Cochrane Review

- **Weak evidence** of benefit on medications in children with FAP

  Huertas-Ceballos A, et al. Cochrane Database Syst Rev. 2008

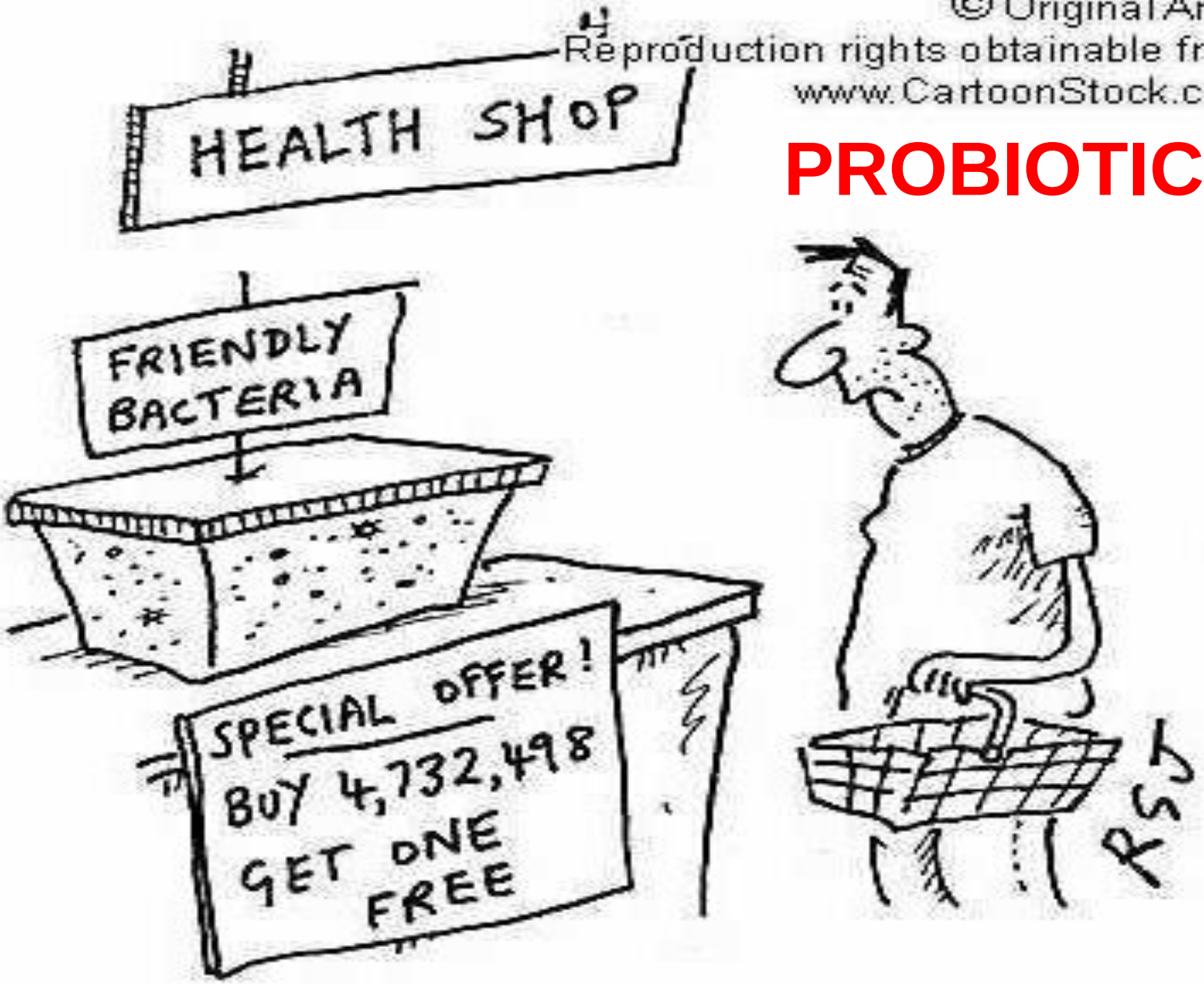
- **No evidence** fiber useful for treating children with FGIDs.

  Horvath A. et al. Ann Nutr Metab. 2012;61:95-101.

- **No evidence** lactose free diets effective functional abdominal pain

  Huertas-Ceballos AA. et al. Cochrane Database Syst Rev. 2009

PROBIOTICS



Probiotics

Horvath A., et al. Aliment Pharmacol Ther. 2011;33:1302-10.

- Meta-analysis- 3 RCTs
- LGG supplementation higher rate of treatment responders (no pain or ⇓ pain intensity)
- AP-FGIDs (NNT=7)
- IBS (NNT=4) (only IBS ⇓ frequency)
- No effect in Functional Dyspepsia and Functional Abdominal Pain

VSL#3 Irritable Bowel Syndrome

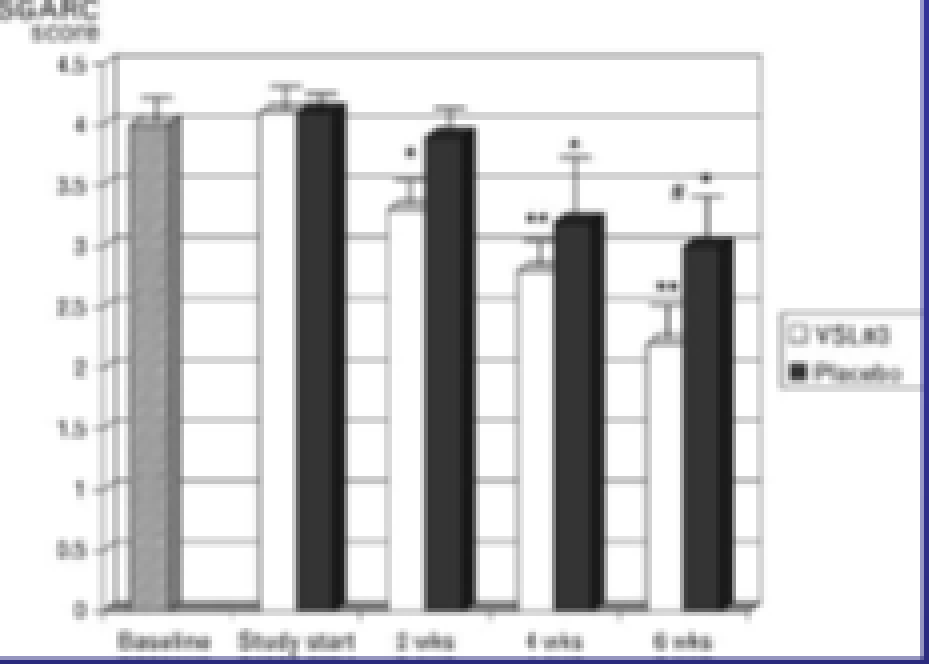
Guandalini S et al. J Pediatr Gastroenterol Nutr. 2010;51:24-30

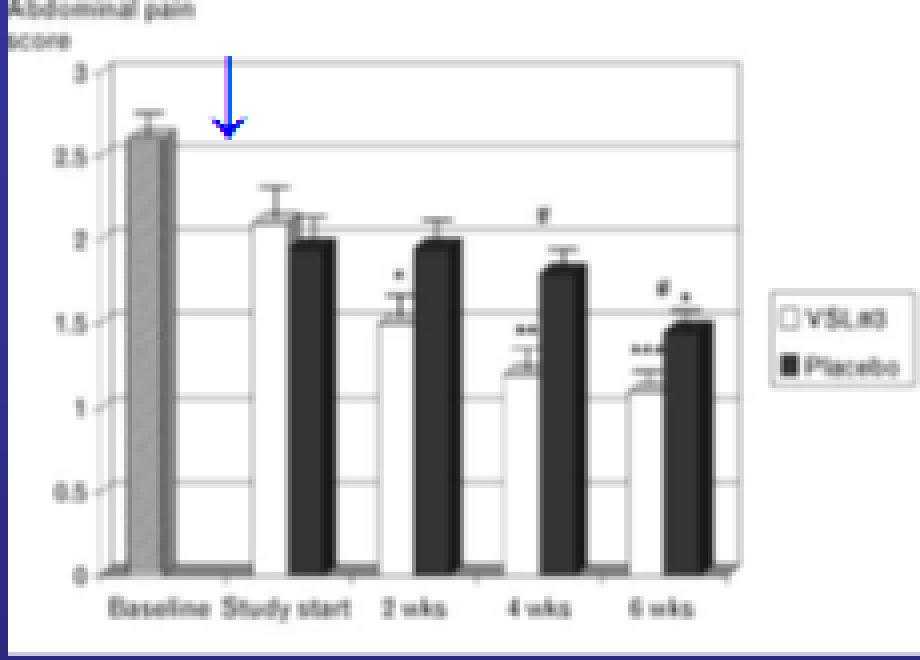
- Randomized, double-blind, placebo-controlled, crossover trial in 5 centers: Italy (4), India (1)
- 4 - 18 years
- 67 enrolled/59 completed

- Randomización VSL#3 vs. placebo (1 sachet of VSL#3 day 4–11 years or 2 day (12–18 years) for 6 weeks.

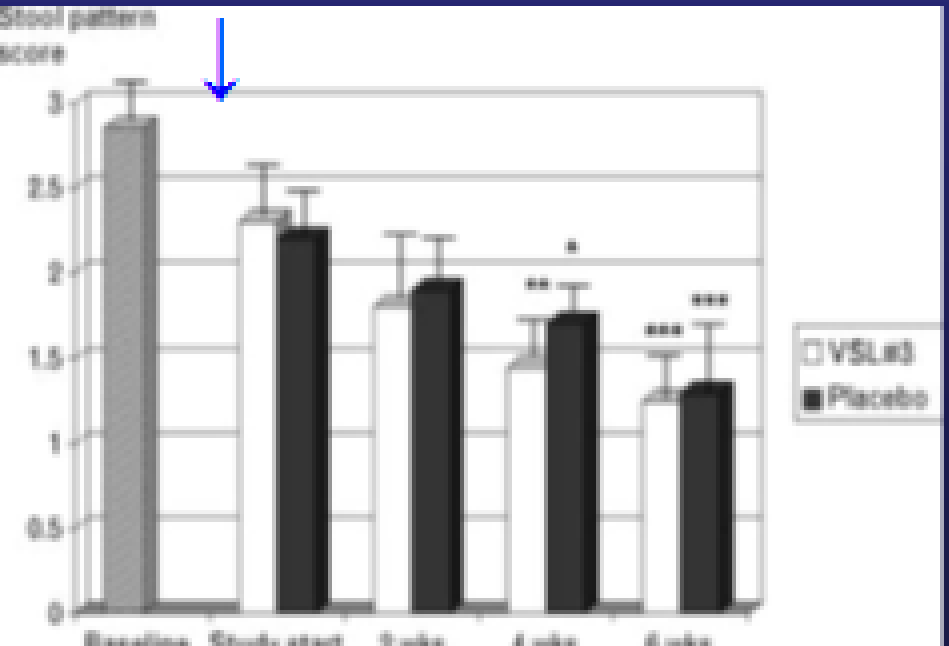
Run-in phase	Randomization VSL#3/Placebo	Washout period	Switched groups
2 weeks	6 weeks	2 weeks	6 weeks

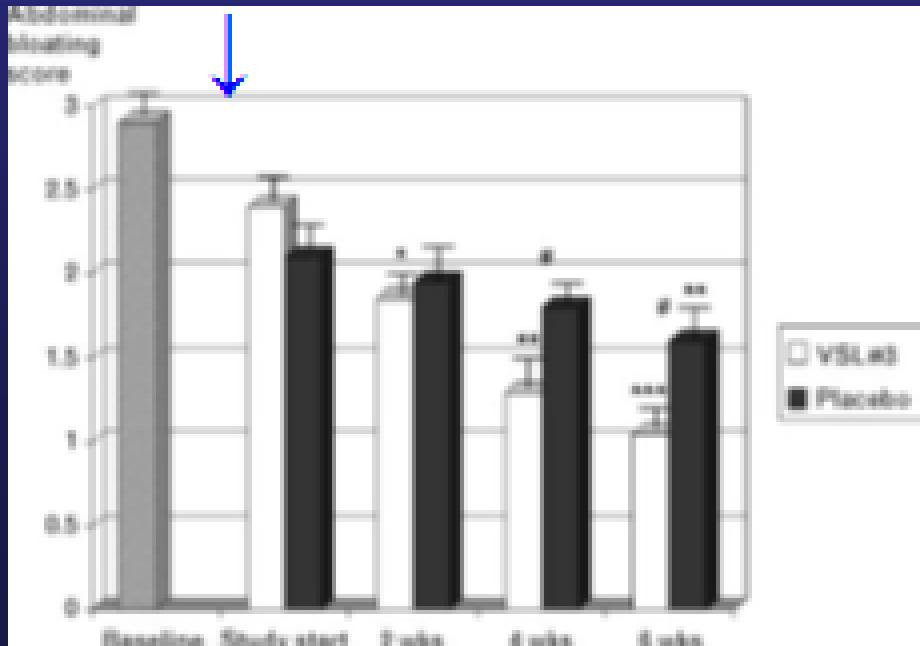
Shulman RJ, et al. J Pediatr Gastroenterol Nutr. 2012 ;54:109;





Are we dedicating enough attention to the patients and their families?





Cognitive Behavioral Therapy

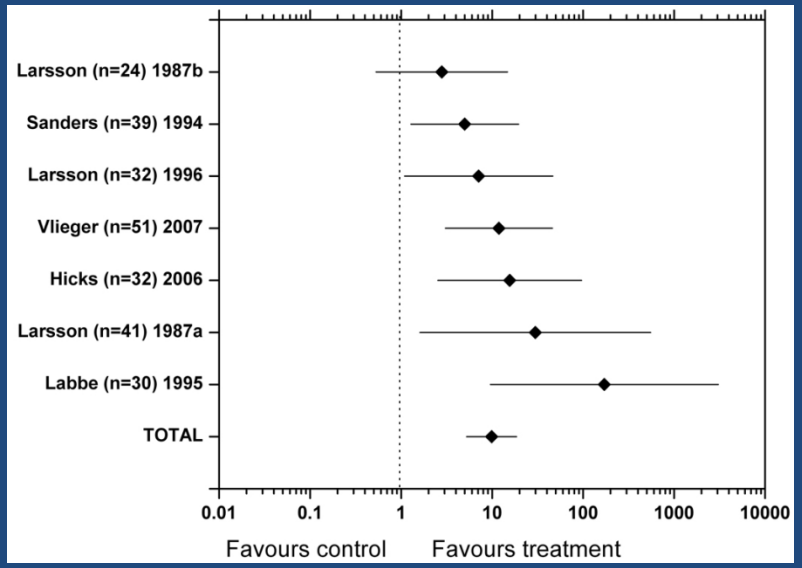
Huertas-Ceballos AA. et al. Cochrane Database Syst Rev. 2009:CD003019.

Evidence to believe that cognitive-behavioral treatment useful for the treatment of abdominal pain in children

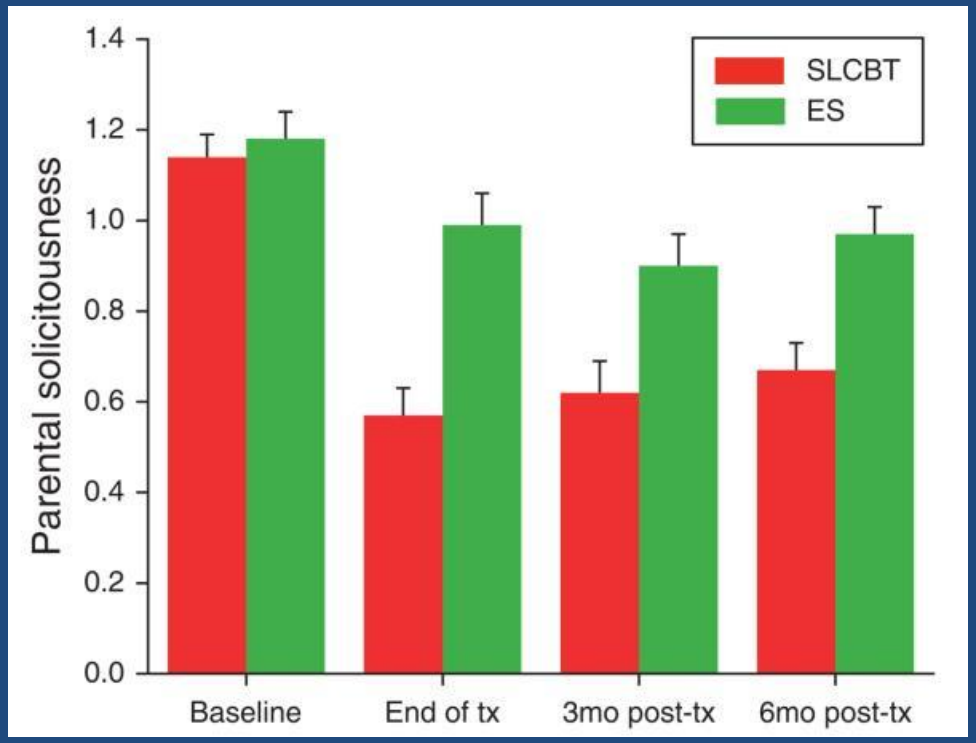
Psychological therapies, as a group, reduced pain by > 50%

Pain. 2010;148: 387–397.

Meta-analysis 25 studies (1247 children) CBT, relaxation therapy, biofeedback significant effects on pain reduction.



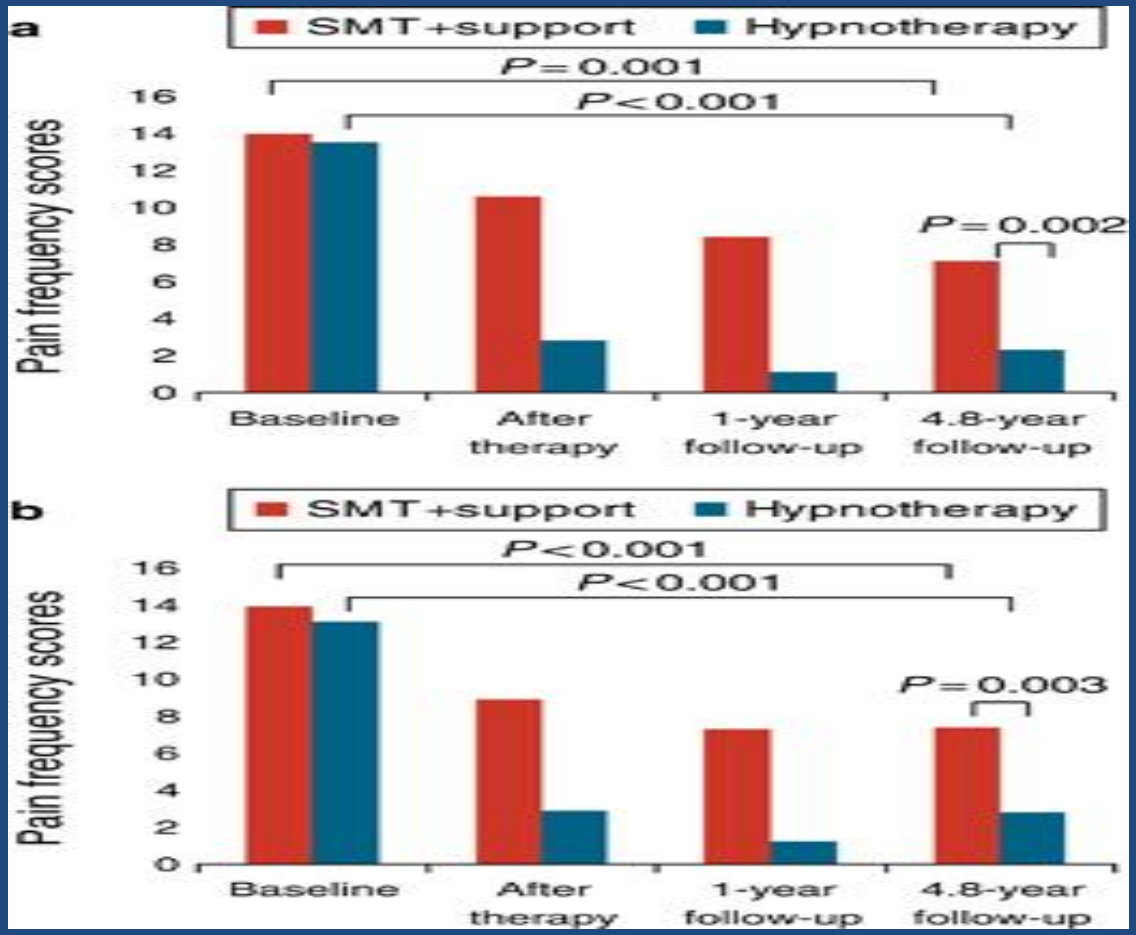
Intervention aimed at altering parental responses to pain and children's ways of coping and thinking about their symptoms



Levy RL, et al. Am J Gastroenterol. 2010;105:946-56.

"When you awaken you will feel fresh and relaxed – with absolutely no memory of changing my lightbulbs."

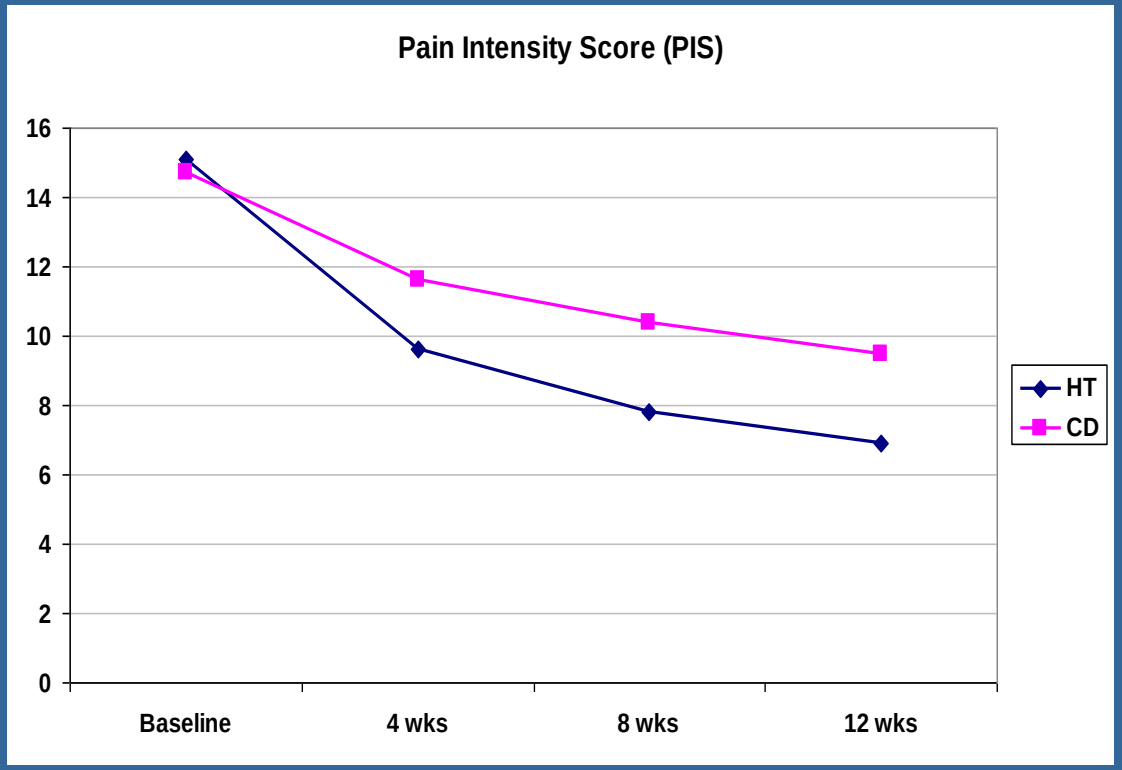
Hypnosis



Am J Gastroenterol 2012; 107:627–631

Rutten JMTM. et al, DDW 2014

To compare the efficacy of individual hypnotherapy performed by a therapist with CD recorded self-exercises at home in children with IBS or FAP(S)



Acupuncture

Lim B. et al. Cochrane Database Syst Rev. 2006;CD005111

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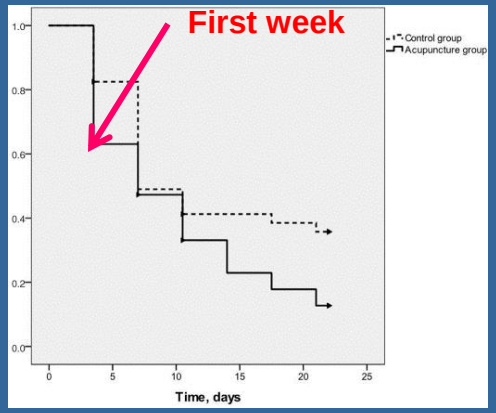
- Poor quality studies. No randomized control studies in children with IBS but …

- Double blinded: Infant colics lenght of cry and irritability < acupunture, < infants met diagnosis (p=0.03)

Landgren K, cols. Acupunct Med. 2010;28:174-9



Brands MM, col. Complement Ther Med. 2011;19:109-14.

- 20 children, 8-18 years, IBS, functional abdominal pain
- 10 sesions yoga
- Abdominal pain less frequent and intense (p=0.004)
- Better quality of life.
- 3 months significant improvement of pain


Dairy Allergy
Peanut Allergy
Soy Allergy
Shellfish Allergy

Fermentable Oligo-Di-Monosaccharides and Polyols

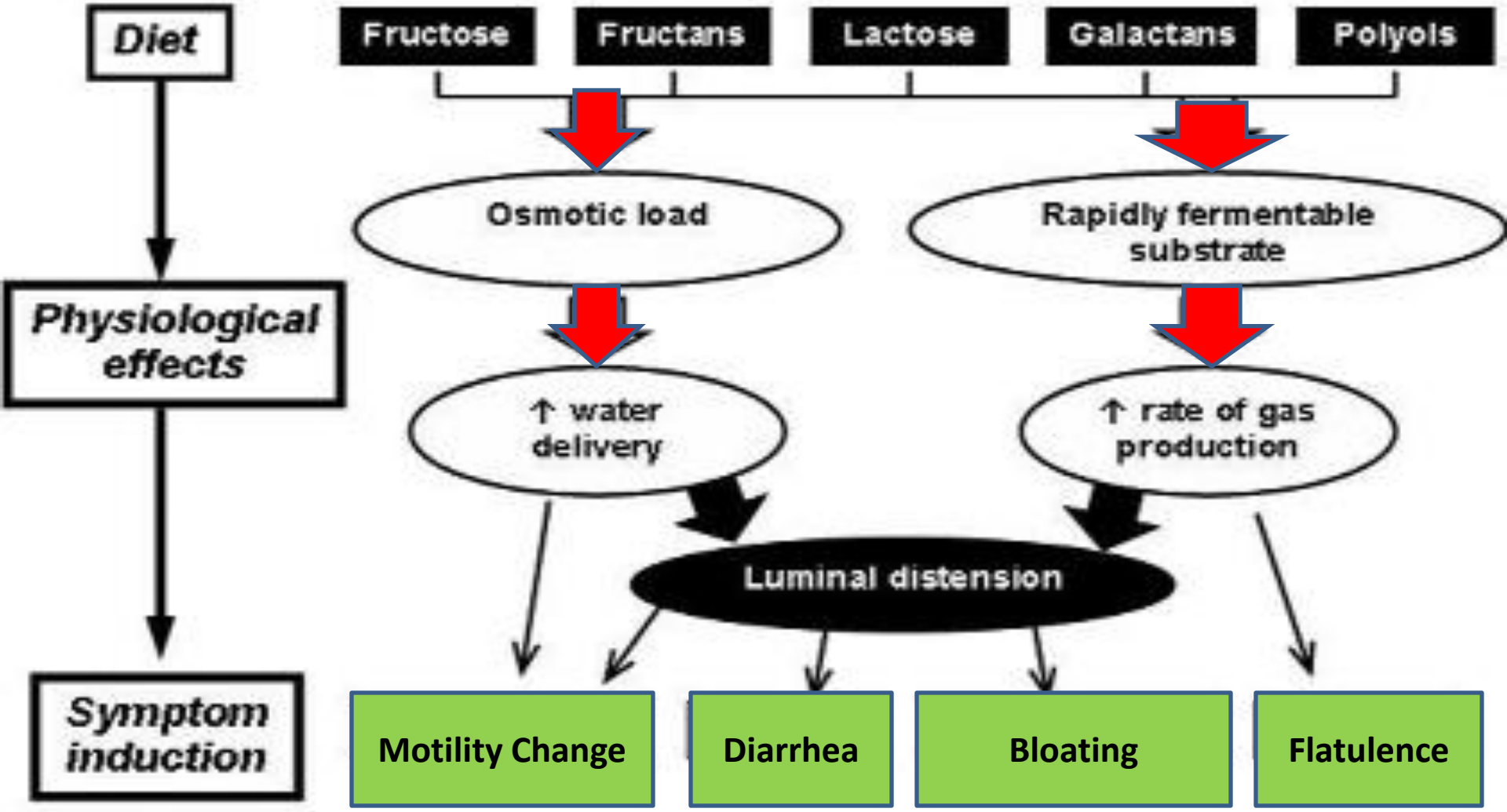
The FODMAPS Diet

excess fructose	lactose	fructans	galactans	polyols
fruit apple, mango, nashi, pear, tinned fruit in natural juice, watermelon **sweetners** fructose, high fructose corn syrup, concentrated fruit sources, large servings of fruit, dried fruit, fruit juice **honey** corn syrup, fruisana	**milk** milk from cows, goats or sheep, custard, ice cream, yogurt **cheeses** soft unripened cheeses, such as cottage cheese, cream, mascarpone, ricotta	**vegetables** asparagus, beetroot, broccoli, brussel sprouts, cabbage, eggplant, fennel, garlic, leek, okra, onion, shallots, spring onion **cereals** wheat and rye **fruit** custard apple, persimmon, watermelon **misc.** chicory, dandelion, inulin	**legumes** baked beans, chickpeas, kidney beans, lentils	**fruit** apple,apricot, avocado, blackberry, cherry, lychee, nashi, nectarine, peach, pear, plum, prune, watermelon **vegetables** cauliflower, bell pepper, mushroom, sweet corn **sweetners** sorbitol, mannitol, isomalt, maltitol, xylitol

FODMAPs - Pathophysiology

Gibson PR, Shepherd SJ. *J Gastroenterol Hepatol* 2010; 25: 252-258

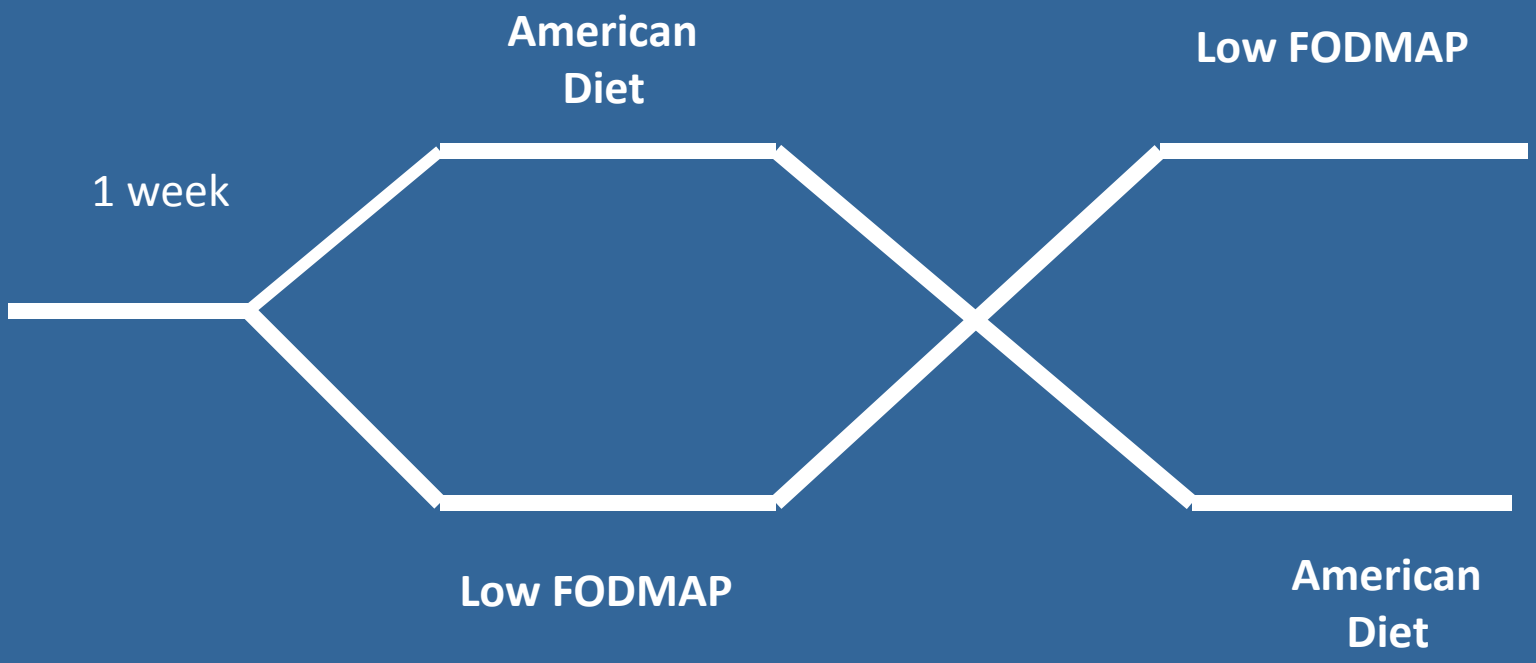
Barrett JS, Gibson PR. *Practical Gastroenterology* 2007; 51-65



LOW FODMAP

Chumpitazi B, et al. Aliment Pharmacol Ther. 2015;42:418-27.

IBS- Rome III



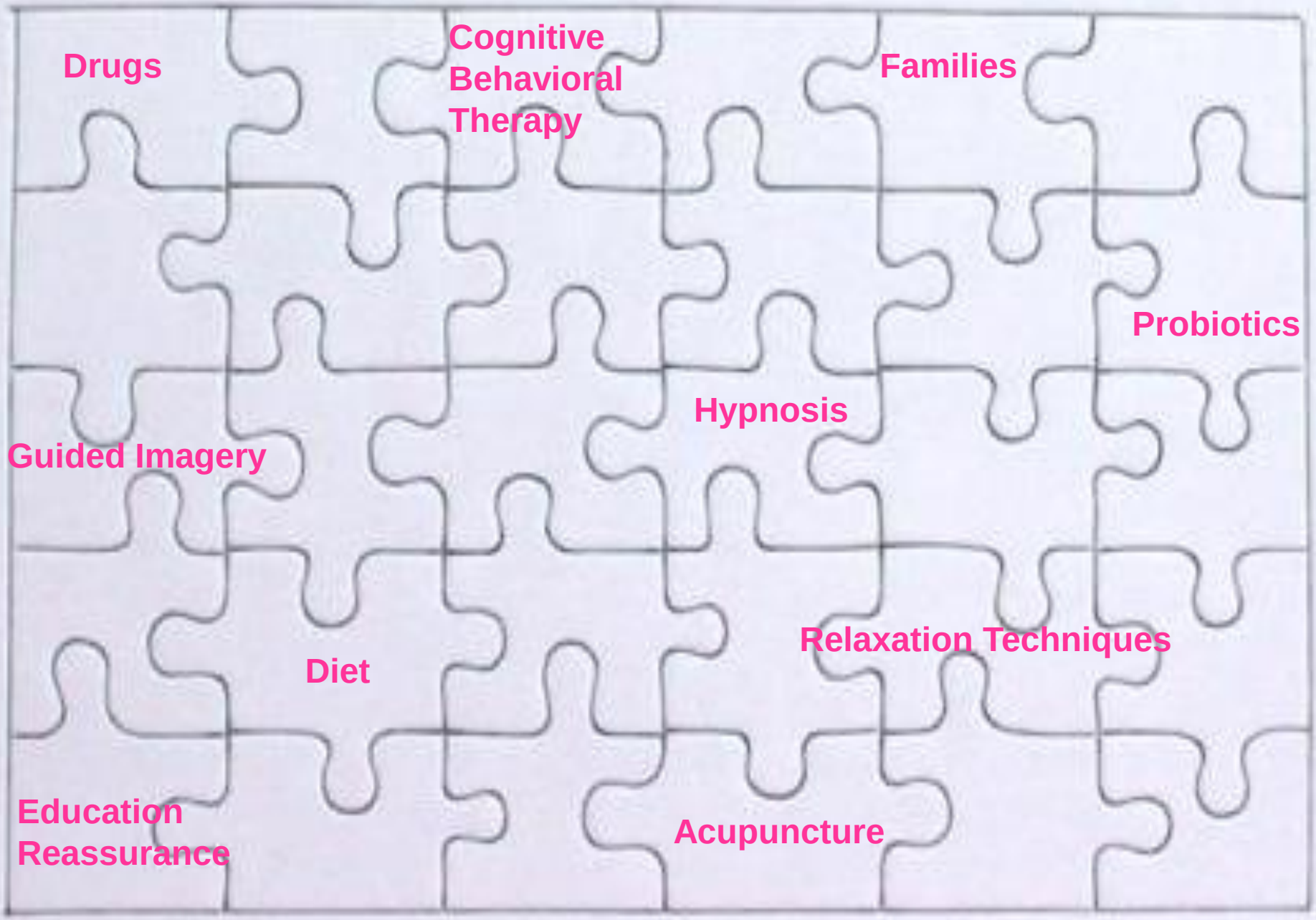
- ↓ abdominal pain during low FODMAP diet [1.1/day vs. 1.7/day $P < 0.05$]
- Compared to baseline- fewer episodes pain (1.4) during low FODMAP diet ($P < 0.01$) but more episodes during the American diet ($P < 0.01$).

Non-Celiac Gluten Sensitivity

Abdominal discomfort or pain, bloating, flatulence and diarrhea

No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates.

Biesiekierski JR et al. Gastroenterology 2013;145:320-8.


Drugs
Cognitive Behavioral Therapy
Families
Probiotics
Hypnosis
Guided Imagery
Relaxation Techniques
Diet
Education Reassurance
Acupuncture

Sleep

Nutrition

Family

Social Worker

Education

Autonomic medicine

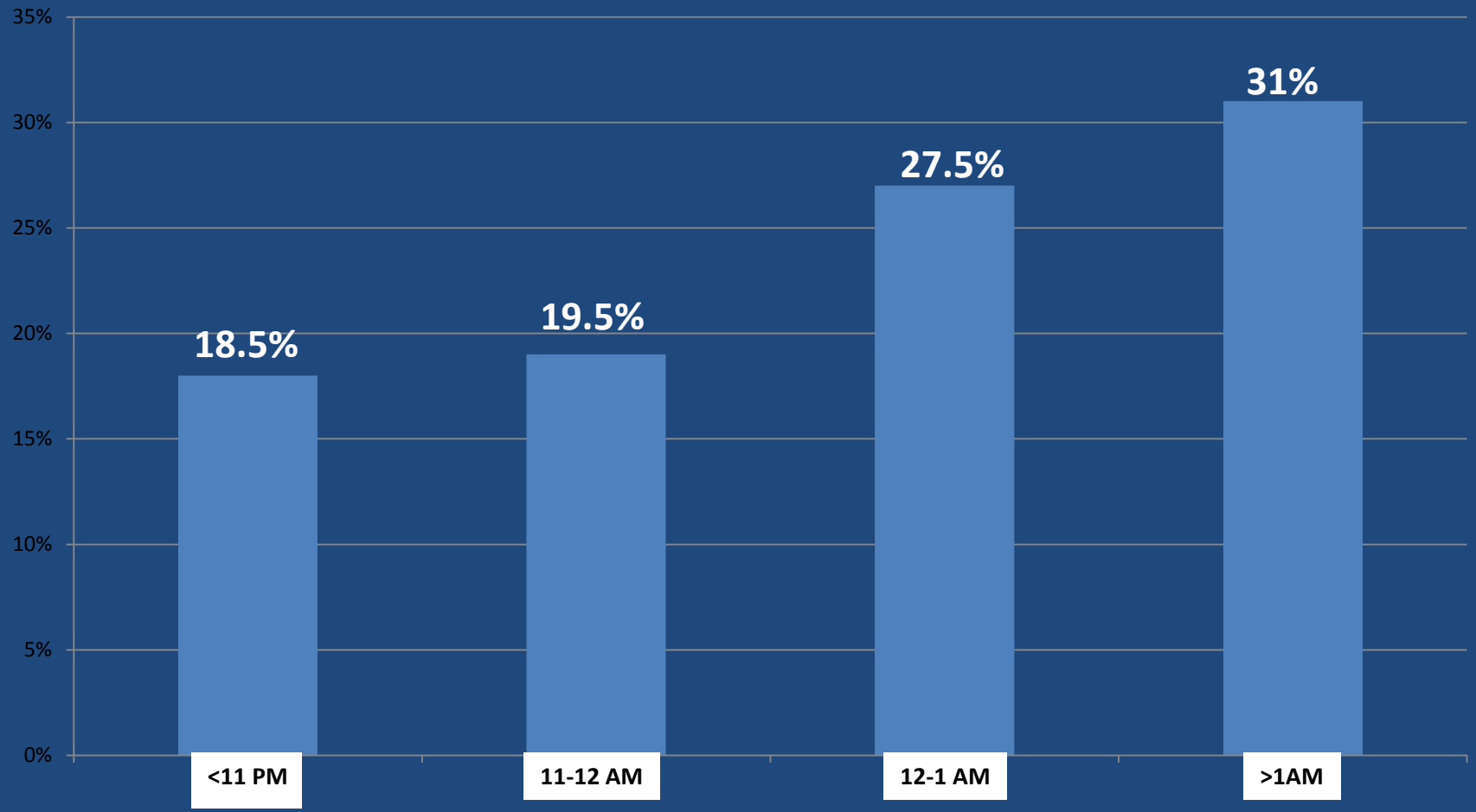
No correlation between abdominal pain and grades

School grades and pain frequency (r=0.04)

School grades and pain intensity (r=0.03)

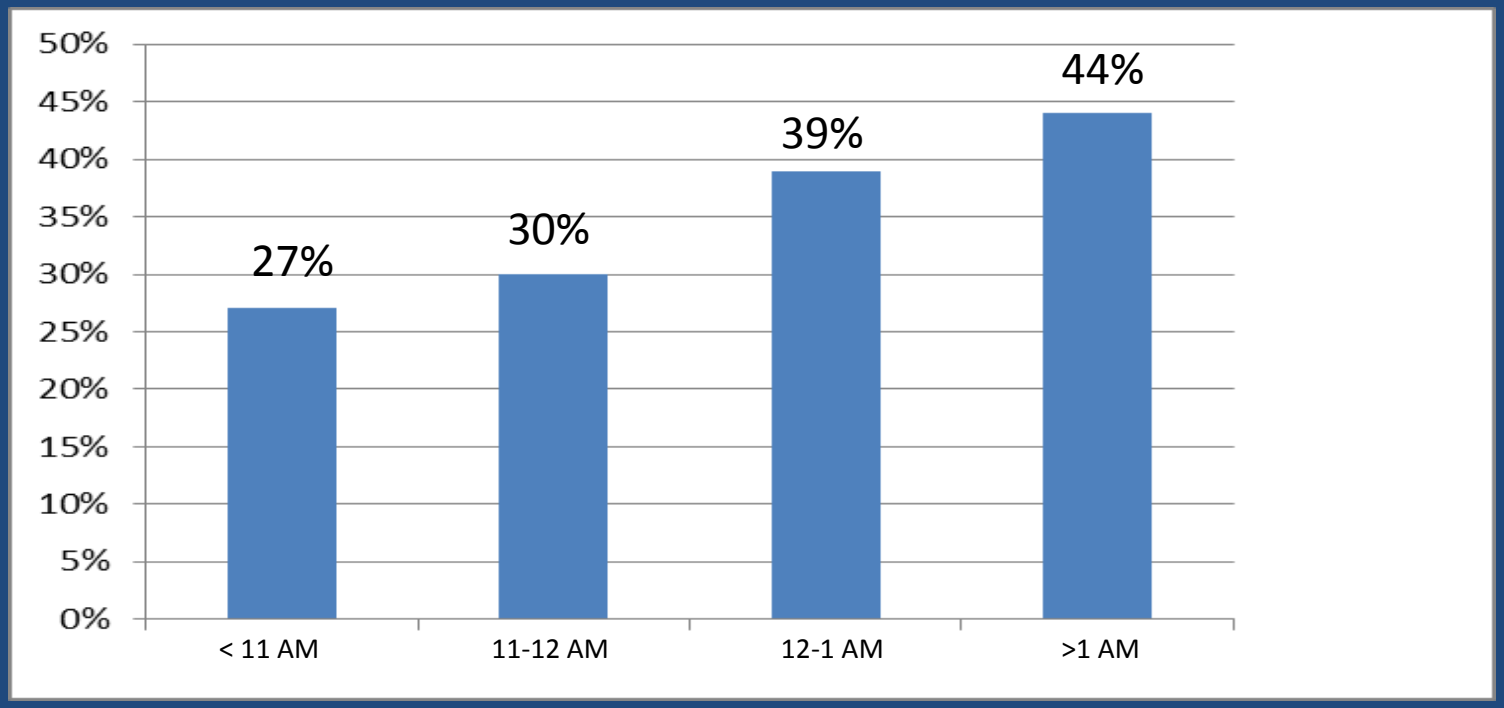
Saps M, et al. J Pediatr Gastroenterol Nutr. 2008.

Prevalence of Abdominal Pain by Time Going To Bed



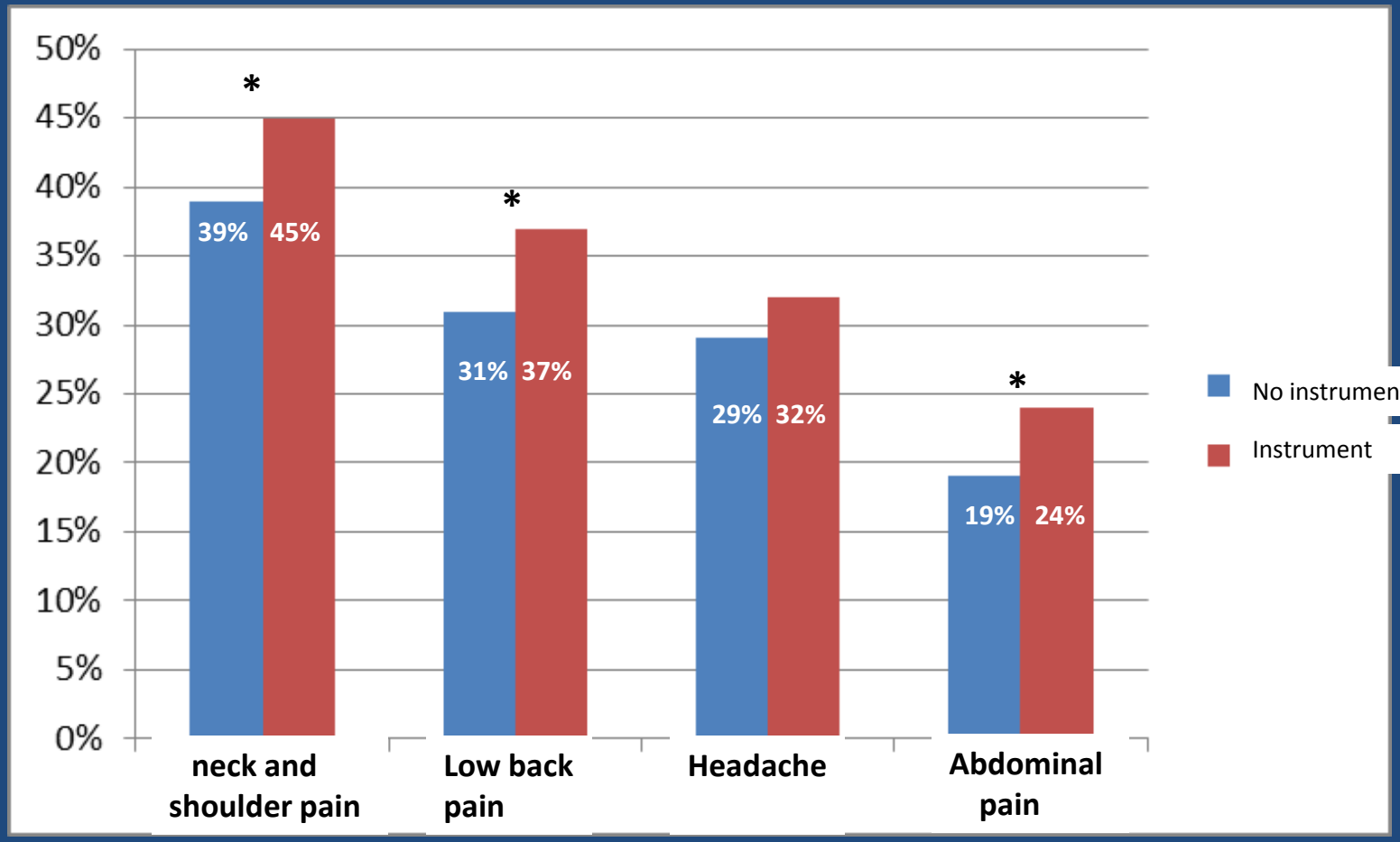
Zhang, et al. BMC Musculoskelet Disord. 2015; 16: 219.

Prevalence of Headache by Time Going To Bed

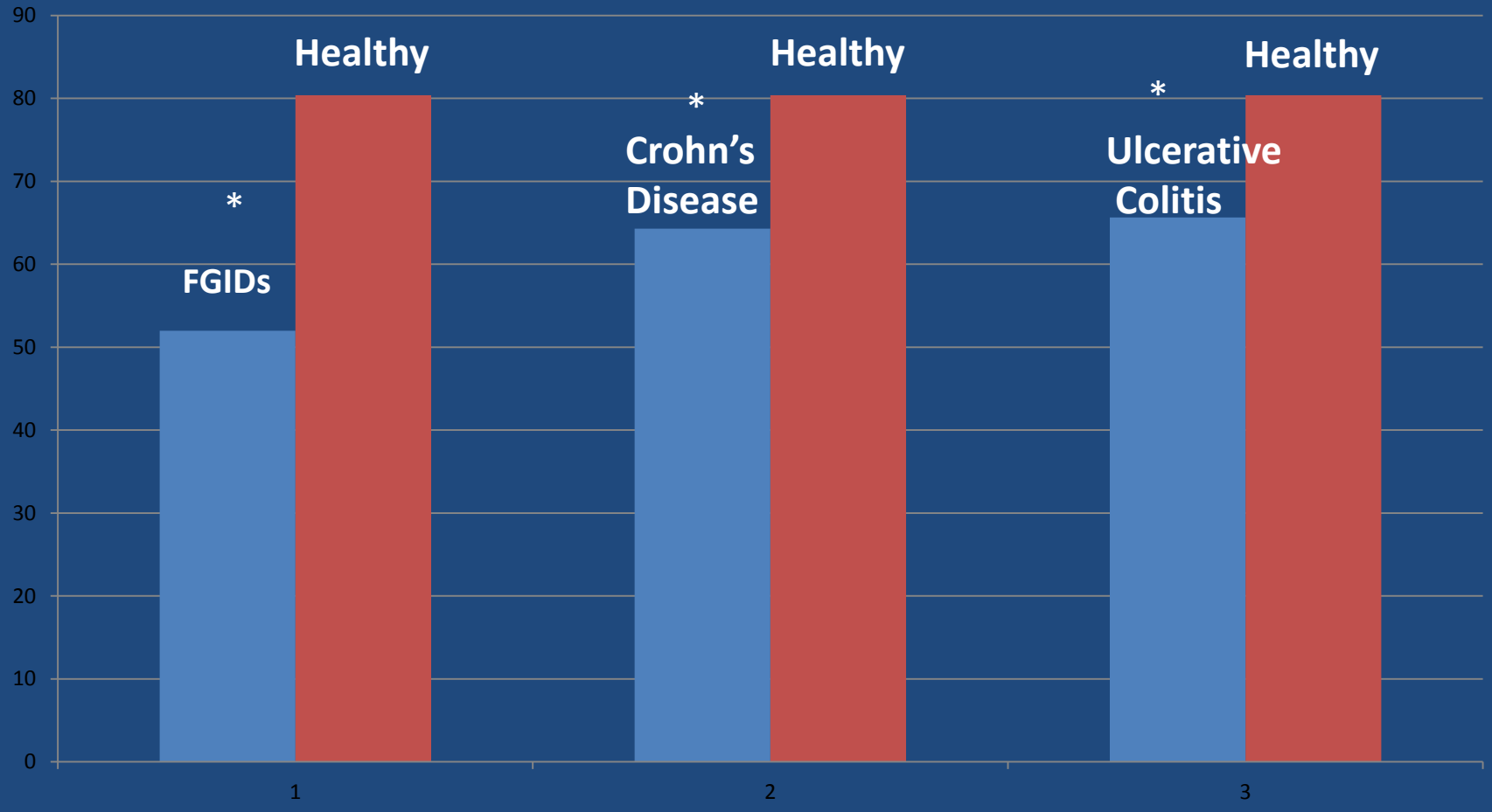


Zhang, et al. BMC Musculoskelet Disord. 2015; 16: 219.

Pain and Playing an Instrument



Headaches
PedsQL Headache Item Scores



Varni et al. Under review

Interference

- Children reporting headaches increased risk of other somatic symptoms (P <0.05)

Pediatric Functional Disability Inventory	
I feel angry	73
I forget things	75
I worry about what will happen to me	77
I feel sad or blue	80
I have trouble sleeping	80

Pain Pract. 2010;10:214-21.

What Do We Do?

- Take the time, reassure and educate
- Explore preferences
- Consider medications
- Consider alternatives

Paradigm

- Identify Who Benefits From Each Intervention
- Evaluate Children Individually
- Make Decisions Based On Literature and Experience
- Provide Comprehensive and Combined Treatments


WHAT IS IN THE HORIZON?

- **Lubiprostone-** stimulates intestinal fluid secretion, through activation of ClC-2-type Cl(-) channels.

Hyman PE, et al. J Pediatr Gastroenterol Nutr. 2014;58:283-91.

- **Prucalopride-** selective, high-affinity 5-HT4 receptor agonist with gastrointestinal prokinetic properties

Winter H, et al. J Pediatr Gastroenterol Nutr. 2013;57:197-203.

Mugie S et al. Gastroenterology. 2014;147:1285-95

Nurko S, Saps M. Gastroenterology. 2014;147:1214-6.

- **Linaclotide-**


Ask No Questions
Hear No Lies!

Peppermint oil- formulation-specific which, in IBS, could increase intestinal residence time of the active ingredient.

Mebeverine

- Smooth-muscle relaxant, anticholinergic activity
- RCT -115 children functional abdominal pain
- Mebeverine (135mg, bid)/placebo- 4 weeks
- Intention to treat: 40.6% vs. 30.3%
- Per protocol: drug 54.5% vs placebo 39.5%
- NON SIGNIFICANT (similar to adult studies)

Pourmoghaddas Z, et al. Biomed Res Int. 2014;2014:191026

Ruepert L, et al. .Cochrane Database Syst Rev. 2011;(8):CD003460

Meta-analysis adults

- Trimebutine improves pain. Mebeverine NSD.

Trimebutine

Karabulut GS, cols. J Neurogastroenterol Motil. 2013;19:90-3.

- Antimuscarinic and opioid agonist
- 78 adolescents tertiary care: trimebutine maleate (3 mg/kg/day, 3 dose day 3 weeks) vs. no treatment
- 95% drug vs. 20% control (P＜0.0001)
- No medication
- Conclusion similar to adult studies

Ruepert L, et al. .Cochrane Database Syst Rev. 2011;(8):CD003460