TREATMENT OF ABDOMINAL PAIN DISORDERS

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Nationwide Children’s Hospital
Disclosures

Scientific Consultant

• QOL Medical
• Forest
• Quintiles
• **Rome Criteria III**


• **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%

### Weekly Prevalence of Symptoms

**USA vs. Colombia**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Colombia n=265</th>
<th>USA (historical data) n=237</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain</td>
<td>35%</td>
<td>38%</td>
<td>NS</td>
</tr>
<tr>
<td>Nausea</td>
<td>25%</td>
<td>23%</td>
<td>NS</td>
</tr>
<tr>
<td>Constipation</td>
<td>11%</td>
<td>8%</td>
<td>NS</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8%</td>
<td>9%</td>
<td>NS</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7%</td>
<td>7%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Non- Gastrointestinal Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headaches</td>
<td>31%</td>
<td>42%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pains Arms Legs</td>
<td>39%</td>
<td>36%</td>
<td>NS</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>25%</td>
<td>15%</td>
<td>0.02</td>
</tr>
<tr>
<td>Abdominal Pain Interference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any activity</td>
<td>56%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gym</td>
<td>19%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>School</td>
<td>14%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep</td>
<td>12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social</td>
<td>11%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

23% missed school (mean 2.3 days)

10% parents miss work (mean 1.9 days)

Abdominal Pain

Functional Gastrointestinal Disorder
FUNCTIONAL ABDOMINAL PAIN DISORDERS
<table>
<thead>
<tr>
<th></th>
<th>Participants</th>
<th>FGIDs</th>
<th>Pain Disorders</th>
<th>IBS</th>
<th>Study Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colombia 1</strong></td>
<td>373</td>
<td>29</td>
<td>11.1</td>
<td>5.4</td>
<td>Saps et al. J Pediatr. 2014</td>
</tr>
<tr>
<td><strong>Colombia 2</strong></td>
<td>3198</td>
<td>27.3</td>
<td>10.2</td>
<td>5.4</td>
<td></td>
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<tr>
<td><strong>Ecuador</strong></td>
<td>417</td>
<td>22.8</td>
<td>10.1</td>
<td>4.8</td>
<td>Koppen IJ, Saps et al. Under review</td>
</tr>
<tr>
<td><strong>Panama</strong></td>
<td>321</td>
<td>28.7</td>
<td>12.2</td>
<td>5.6</td>
<td>Lu P, Saps et al. Under review</td>
</tr>
<tr>
<td><strong>El Salvador</strong></td>
<td>399</td>
<td>20.3</td>
<td>9.2</td>
<td>3.8</td>
<td>Zablah, Bonilla S, Saps et al. Rev Gastroenterol Mex. 2015</td>
</tr>
<tr>
<td><strong>USA</strong></td>
<td>507</td>
<td></td>
<td></td>
<td>6</td>
<td>Hyams JS, et al.</td>
</tr>
</tbody>
</table>
Pain episode

Risk factors: Genetics, Gender, Early life events

Appraisal of Pain Episode

Coping with Pain Episode

Episode Outcome

Maladaptive response

Psychosocial stressors

Infection / inflammation

Protection factors: Culture, Gender, Social support

Chronic Pain

Potential long-term outcomes

Normal development

# Health-Related Quality of Life

<table>
<thead>
<tr>
<th></th>
<th>AP-FGIDs Rome III</th>
<th>Controls</th>
<th>FAP Rome II</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sri-Lanka</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>84</td>
<td>91</td>
<td>82</td>
<td>86</td>
</tr>
<tr>
<td>Social</td>
<td>85</td>
<td>93</td>
<td>86</td>
<td>88</td>
</tr>
<tr>
<td>Emotional</td>
<td>74</td>
<td>83</td>
<td>76</td>
<td>81</td>
</tr>
<tr>
<td>School</td>
<td>75</td>
<td>82</td>
<td>74</td>
<td>81</td>
</tr>
<tr>
<td>Overall scores</td>
<td>80</td>
<td>88 *</td>
<td>80</td>
<td>86</td>
</tr>
<tr>
<td><strong>USA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Devanarayana NM et al. BMC Gastroenterol. 2014 21;14:150*  

*p < 0.001*
Health-related quality of life (HRQOL)


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

2-4 % seek medical attention for abdominal pain

Total mean cost per discharge for a child with FGIDs increased from $6115 to $18058 from 1997 to 2009.

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


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
ONE consultation for abdominal pain
3.8% of the per capita health care spending in Uruguay

Comorbidities


- 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

![Bar chart showing adult outcomes of FAP for Psych disorders, Anxiety disorders, and Psych meds.]

**Campo JV et al. Pediatrics 2001; 108: E1**
Drugs


Challenges of caring for children with functional gastrointestinal disorders.

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

The use of non-narcotic pain medication in pediatric gastroenterology

Antispasmodics

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, prifinimum, propinox.

• NONE USA
Antispasmodics

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

Cyproheptadine


- 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
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

<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Side effects</td>
<td>30%</td>
<td>32%</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>16%</td>
<td>12%</td>
</tr>
<tr>
<td>Increase appetite</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Weight gain</td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>Irritability</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2.5%</td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to side effects</td>
<td>2.5%</td>
<td>15%</td>
</tr>
</tbody>
</table>
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
<table>
<thead>
<tr>
<th></th>
<th>IBS-associated diarrhea</th>
<th>Periumbilical pain</th>
<th>RLQ pain</th>
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<tbody>
<tr>
<td><strong>Week 6</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMI</td>
<td>$-50 \pm 12.9$</td>
<td>$-18.8 \pm 10.1$</td>
<td>$-25 \pm 14.4$</td>
</tr>
<tr>
<td>Placebo</td>
<td>$-11.8 \pm 11.8$</td>
<td>$5.9 \pm 10.4$</td>
<td>$17.6 \pm 9.5$</td>
</tr>
<tr>
<td>$P$ value</td>
<td>.029</td>
<td>.089</td>
<td>.014</td>
</tr>
<tr>
<td><strong>Week 10</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMI</td>
<td>$-50 \pm 12.9$</td>
<td>$-12.5 \pm 8.5$</td>
<td>$-12.5 \pm 8.5$</td>
</tr>
<tr>
<td>Placebo</td>
<td>$-11.8 \pm 11.8$</td>
<td>$17.6 \pm 9.5$</td>
<td>$11.8 \pm 8.1$</td>
</tr>
<tr>
<td>$P$ value</td>
<td>.029</td>
<td>.018</td>
<td>.039</td>
</tr>
<tr>
<td><strong>Week 13</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMI</td>
<td>$-37.5 \pm 12.5$</td>
<td>$-12.5 \pm 12.5$</td>
<td>$-25 \pm 11.2$</td>
</tr>
<tr>
<td>Placebo</td>
<td>$-11.8 \pm 11.8$</td>
<td>$17.6 \pm 9.5$</td>
<td>$17.6 \pm 9.5$</td>
</tr>
<tr>
<td>$P$ value</td>
<td>.134</td>
<td>.055</td>
<td>.004</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th></th>
<th>Amitriptyline</th>
<th>Placebo</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better</td>
<td>63%</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>Good/Excellent</td>
<td>53%</td>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>

Significant improvement of pain ($p<0.0001$). Trend difference between groups ($p=0.90$).
## Intention to Treat vs. Per Protocol


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

### Table: Intention to Treat vs. Per Protocol

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Amitriptyline</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failed</td>
<td>17%</td>
<td>16 %</td>
<td>17.5 %</td>
</tr>
<tr>
<td>Poor</td>
<td>12%</td>
<td>16 %</td>
<td>7.5 %</td>
</tr>
<tr>
<td>Mild</td>
<td>19 %</td>
<td>14%</td>
<td>25 %</td>
</tr>
<tr>
<td>Good</td>
<td>40%</td>
<td>37%</td>
<td>53%</td>
</tr>
<tr>
<td>Excellent</td>
<td>12 %</td>
<td>16 %</td>
<td>7.5 %</td>
</tr>
</tbody>
</table>

### Results:

- Total: 146
- Amtriptyline: 146
- Placebo: 146

- Failed: 17% vs. 17.5%
- Poor: 12% vs. 7.5%
- Mild: 19% vs. 25%
- Good: 40% vs. 53%
- Excellent: 12% vs. 7.5%
Citalopram

Campo et al.

Roofhaza H, et al NGM 2014
Rifaximin 600 mg/day effective and safe for the treatment of bacterial overgrowth and irritable bowel syndrome in children
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


- 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
  

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

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

HEALTH SHOP

FRIENDLY BACTERIA

SPECIAL OFFER!
BUY 4,732,498
GET ONE FREE
Probiotics


- 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


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

<table>
<thead>
<tr>
<th>Run-in phase</th>
<th>Randomization VSL#3/Placebo</th>
<th>Washout period</th>
<th>Switched groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks</td>
<td>6 weeks</td>
<td>2 weeks</td>
<td>6 weeks</td>
</tr>
</tbody>
</table>

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


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%.

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

“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
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**


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

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

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

Dairy Allergy
Peanut Allergy
Egg Allergy
Soy Allergy
Shellfish Allergy
Wheat Allergy
<table>
<thead>
<tr>
<th>Excess Fructose</th>
<th>Lactose</th>
<th>Fructans</th>
<th>Galactans</th>
<th>Polyols</th>
</tr>
</thead>
</table>
FODMAPs - Pathophysiology

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

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

- Motility Change
- Diarrhea
- Bloating
- Flatulence
LOW FODMAP


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.

What Do We Do With These Data?

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

Prevalence of Abdominal Pain by Time Going To Bed

- <11 PM: 18.5%
- 11-12 AM: 19.5%
- 12-1 AM: 27.5%
- >1 AM: 31%

Prevalence of Headache by Time Going To Bed

Pain and Playing an Instrument

- Neck and shoulder pain: 39% (No instrument), 45% (Instrument)
- Low back pain: 31% (No instrument), 37% (Instrument)
- Headache: 29% (No instrument), 32% (Instrument)
- Abdominal pain: 19% (No instrument), 24% (Instrument)
Headaches

PedsQL Headache Item Scores

Varni et al. Under review
Interference

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

<table>
<thead>
<tr>
<th>Pediatric Functional Disability Inventory</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>I feel angry</td>
<td>73</td>
</tr>
<tr>
<td>I forget things</td>
<td>75</td>
</tr>
<tr>
<td>I worry about what will happen to me</td>
<td>77</td>
</tr>
<tr>
<td>I feel sad or blue</td>
<td>80</td>
</tr>
<tr>
<td>I have trouble sleeping</td>
<td>80</td>
</tr>
</tbody>
</table>

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.
  

• **Prucalopride**- selective, high-affinity 5-HT4 receptor agonist with gastrointestinal prokinetic properties
  
  Mugie S et al. Gastroenterology. 2014;147:1285-95

• **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)


Meta-analysis adults

• Trimebutine improves pain. Mebeverine NSD.
Trimebutine


• 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