Pharmacological Treatments for Chronic Abdominal Pain—what you see is not what you get

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-I am a consultant to QOL Medical
-No other financial relationships with any commercial entity to disclose

Objectives:
- Review clinical trials in children with chronic abdominal pain
- Understand the potential targets for pharmacological therapy
- Review current treatment options

A brief word about abdominal pain prevalence

Demographics
Male 43% 25%
Female 57% 36%
Average age (range), years 11.8 (8-15)
Average age of boys 11.7
Average age of girls 11.9
African-American 33% 30%
Latino 22% 32%
Caucasian 21% 33%
Other 16% 35%
Asian 6% 42%

*Saps M et al., J Pediatr. 2009

Why is There No Algorithm for Treatment?
- Not enough data to support decision tree
- Phenotype is not well understood
- Mechanism of disease and medications not well understood
- Very few clinical trials in children

How far Have We Really Come?
1959
55 years
8 randomized, controlled trials (4 positive)
421 children studied
Clinical Trials in Children with Abdominal Pain

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Duration</th>
<th>Age (Mean)</th>
<th>Primary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rome II criteria for IBS</td>
<td>8 weeks</td>
<td>14.7 years</td>
<td>Improvement in overall QOL score (6, 10, and 13 weeks)</td>
</tr>
<tr>
<td>Rome II criteria for IBS, FD, FAP, AM</td>
<td>10 days</td>
<td>12.7 years</td>
<td>1) Individual GI Symptoms 2) Overall Symptom Improvement</td>
</tr>
<tr>
<td>Manning or Rome I criteria for IBS</td>
<td>2 weeks</td>
<td>12.0 years</td>
<td>1) Symptom Improvement 2) Mean Pain Severity</td>
</tr>
<tr>
<td>Rome II criteria for FAP</td>
<td>2 weeks</td>
<td>7.5 years</td>
<td>1) Change in Pain Frequency 2) Change in Pain Intensity</td>
</tr>
<tr>
<td>Rome II criteria for FAP, FD, IBS</td>
<td>4 weeks</td>
<td>12.7 years</td>
<td>1) Satisfactory Relief 2) Satisfaction with Treatment</td>
</tr>
<tr>
<td>Apley's criteria for RAP</td>
<td>6 weeks</td>
<td>10.5 years</td>
<td>1) Abdominal Pain Score 2) Global Assessment</td>
</tr>
<tr>
<td>Abdominal Migraine for at least six months</td>
<td>16 weeks</td>
<td>Not Provided</td>
<td>1) Days of Abdominal Pain 2) Index of Severity</td>
</tr>
<tr>
<td>Rome III criteria for FAP</td>
<td>4 weeks</td>
<td>10.4 years</td>
<td>Change in Pain Intensity</td>
</tr>
</tbody>
</table>

Why we can’t believe all clinical trials?

Patient A:
15 y/o with 22 month history of chronic abdominal pain
- pain daily, 9/10
- nausea and lightheaded daily, struggles to get out of bed with fatigue
- has missed 28 days of school this year

Patient B:
10 y/o with 3 month history of chronic abdominal pain
- pain 4 days per week 3/10 on scale
- pain only at night
- no nausea or fatigue
- has not missed school or activities

Both fit criteria for enrollment in FAP clinical trial

What Animal Are We studying?

It's Not Just Pain We Have to Address

- Bloating
- Headaches
- Fatigue
- Sleep disruption
- Nausea
- Dizziness with postural changes
- Early satiety
- Anxiety

Can we link it all together?

Proposed Underlying Mechanisms for Chronic Functional Abdominal Pain

- Bacterial Overgrowth
- Neuronal Sensitization
- Descending Pain Modulation
- Autonomic Dysfunction
- Carbohydrate Intolerance
- Motility Disorder
- Altered HPA-axis
- Altered Receptor Expression (5HT, NMDA, TRPV1)
- Dysautonomia
- Genetics
- Anxiety
- Adverse early life
- Sleep
- Stress
- Microbiome
- Epigenetics

Abdominal Pain
Ventral PAG stimulation

- Project to hypothalamus, amygdala, PFC, peri-aqueductal grey (PAG) and locus coeruleus (LC)
- Regulate emotional, autonomic and behavioral responses

Gut Vagal Afferents Differentially Modulate Innate Anxiety and Learned Fear

- Efferent activity is measured non-invasively via HRV
- Afferents may modulate adrenal medullary factors: epi, norepi, dopamine, endogenous opioids, substance P

Khasar et al. 2003

Psychological Therapy

  Walker LS et al., 2006
- Cognitive-behavioral therapy for children with functional abdominal pain and their parents decreases pain and other symptoms.
  Levy RL et al., 2010
- A randomized controlled trial of a cognitive-behavioral family intervention for pediatric recurrent abdominal pain.
  Roberts PM et al., 2005
Responding to Placebo Does Not Make You “Crazy”

- Perform distracting tasks activate PAG, parts of ACC, and orbitofrontal cortex
- Placebo activates endogenous opioids and induces mild respiratory depression and decreases adrenergic activity

Benedetti F et al., J Neurosci. 2005
Pollo et al., Pain 2003

Treatment used for FAP

Pollo et al., Pain 2003

Pharmacological Treatment Options

<table>
<thead>
<tr>
<th>Mild Pain (no disability)</th>
<th>Pain (with disability)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peppermint oil</td>
<td>TCAs (amitriptyline)</td>
</tr>
<tr>
<td>Iberogast</td>
<td>SSRIs (citalopram)</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Probiotics</td>
<td>Antispasmodics (hyoscyamine, dicyclomine)</td>
</tr>
<tr>
<td>Acid suppression</td>
<td>Cyproheptadine</td>
</tr>
<tr>
<td></td>
<td>Rifaximin</td>
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</tbody>
</table>

Constipation
- Linaclotide
- Lubiprostone

Don’t Forget to Ask the Important Question that will Dictate Therapy?

How many days of school or activities have you missed?

Schurman et al., J Pediatr Gastroenterol Nutr. 2010

Medication for Functional Abdominal Pain in Children

Schurman et al., J Pediatr Gastroenterol Nutr. 2010

Amitriptyline

Study in Children
- RCT in adolescents 8 weeks of 10, 20 or 30mg based on weight (n=33)
- Improvement in QOL and pain over placebo
- Negative placebo effect for pain

Mechanism
- Inhibits Na channels, endogenous opioids, NMDA antagonist, anxiolytic.

Dose:
0.1-2mg/kg/d at bedtime

Side Effects
- Constipation, dry mouth, dizziness, somnolence
IBS, FAP and FD patients were randomized to 4 weeks of placebo or amitriptyline
- Dose: (10 mg/d, <35 kg, 20 mg/d, >35 kg)
- Pain was assessed daily with self-report diaries
- No better than placebo in improving abdominal pain
- Reduced anxiety scores (P < 0.0001) compared to placebo

Saps et al., Gastroenterology. 2009

Citalopram
- 12-week open label, flexible dose-trial in children with RAP
- Initial dose 10mg and increase to 40 mg if no response by week 4

Methodological limitation:
- not placebo controlled or blinded
- small group size (n=25)

Campo JV et al., 2004

Citalopram Study in Children
- RCT of 20mg/day vs. placebo for 4 weeks in children with FAP based on Rome III

Roohafza et al., Neurogastroenterol Motil. 2014

Gabapentin
- Increased rectal compliance in adult IBS-D
- Attenuated rectal mechanosensitivity

Mechanism
- Binds alpha 2 delta receptors of Ca channels in CNS (spinal cord, PAG etc.)

Dose: 8-35mg/kg/d divided 3x/daily (max 3600mg/d)

Side Effects
- dizziness, somnolence, fatigue, ataxia


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


- 10-day course of 550 mg of rifaximin vs. placebo TID
- No difference in symptoms, including pain
- Adult studies show a therapeutic gain over placebo about 9-12%

Mechanism
- Alteration in the quantity, location, or quality of the hosts’ intestinal microbiota

Dose: 8-35mg/kg/d divided 3x/daily (max 3600mg/d)

Side Effects
- dizziness, somnolence, fatigue, ataxia


Cyproheptadine for the Treatment of Functional Abdominal Pain in Childhood: a double-blinded randomized placebo-controlled trial


- Pain assessed at 1 and 2 weeks (n=29)
- Improvement (87%) vs. placebo (43%)
- Primary outcome measure was the self-reported change of frequency and duration of abdominal pain
- Did not use validated questionnaires

Mechanism
- Antagonist of serotonin, histamine and muscarinic receptors
- Improved gastric accommodation through 5HT receptors

Dose: 0.25-0.5mg/kg/d divided 2-3x/daily

Side Effects
- Weight gain, somnolence, irritability
Safety and Efficacy of Cyproheptadine for Treating Dyspeptic Symptoms in Children


Study: Retrospective, open label study of 80 children with dyspepsia

Cohort: GER, post fundoplication, diabetes, mitochondrial dysfunction, post Ladd’s procedure

Complementary and Alternative Therapy

- Approximately 12% of non-clinical population seeks complementary therapies for their children with pain
- Nearly all parents express interest in obtaining a “natural” complementary therapy

-McClellan et al., 2008

Melatonin Improves Pain and Decreases Activity of Spinal Neurons

Melatonin Improves Bowel Symptoms in Female Patients with Irritable Bowel Syndrome: a double-blind placebo-controlled study

Lu WZ, Gee KA, Moochhalla S, Ho KY.

Therapeutic effect of melatonin in patients with functional dyspepsia.

Klipinska G, Poplawski T, Drzewoski J, Harasiuk A, Reiter RJ, Blasiak J, Chojnacki J

Influence of melatonin on symptoms of irritable bowel syndrome in postmenopausal women.


(STW 5) Iberogast

- 9 plant extracts: Chamomile flowers, bitter candytuft, angelica root, caraway fruits, milk thistle, lemon balm leaves, greater celandine, licorice root, and peppermint leaves

Mechanism

Likely anti-hyperalgesic properties, improve proximal gastric accommodation, and may have pro-secretory and anti-spasmodic properties

Dose

10 drops (1 ml) before each meal

Cost: 100ml for $32

Side effects

Abdominal cramps, diarrhea, nausea, dizziness

Treatment of Irritable Bowel Syndrome with Herbal Preparations: results of a double-blind, randomized, placebo-controlled, multi-center trial


- RCT in children with IBS (n=42)
- pH-dependent, enteric-coated capsules (<45kg 1 cap; >45kg 2 cap)
- Reduction in abdominal pain severity in 75%

**Mechanism**
Ca+ channel blocker (antispasmodic)

**Dose**
(30-45kg) 187mg 3x/daily, (>45kg) 374mg 3x/daily

**Side Effects**
Heartburn, headache, flushing

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Role of Exercise in Pain Control

**Rat model:**
- Exercise increased β-endorphin and met-enkephalin in RVM and mid-brain PAG
- Ameliorated thermal and tactile hypersensitivity

**Adult IBS**
- Prospective, randomized, controlled, open-label study of 12 weeks (n=102)
- 20–60 min of moderate-to-vigorous intensive physical activity 3 to 5 days per week
- IBS scores, physical functioning, emotion, sleep, energy, and social role were significantly improved

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Conclusions

- Current studies in children with chronic abdominal pain are difficult to interpret
- There is an urgent need to standardize protocols and carry out more studies in children
- Careful evaluation should include assessment of decreased functioning in order to target therapy
- We must take advantage of the placebo effect in the less severe patients and encourage healthy lifestyles