

## 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	AP prevalence
Male	43%	29%
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	8%	42%

\*278 subjects with weekly questionnaires for 1 year

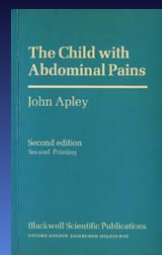
Saps M et al., J Pediatr. 2009

## 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

Randomized, Control Trial	Inclusion Criteria	Duration of Trial	Age (Mean)	Primary Outcomes	Positive/Negative
Amitriptyline satur, 2005	Rome II criteria for IBS	8 weeks	14.7 years	Improvement in overall QoL score (6, 10, and 13 weeks)	Positive
Rifaximin Giles, 2011	Rome II criteria for IBS, FD, FAP, AM	10 Days	12.7 years	1) Individual QoL Symptoms 2) Overall Symptom Burden/Improvement	Negative
Peppermint oil Wain, 2005	Manning or Rome I criteria for IBS	2 Weeks	12.0 years	1) Symptom Improvement 2) Mean Pain Severity	Positive
Cyproheptadine Cummings, 2004	Rome II criteria for FAP	2 Weeks	7.5 years	1) Change in Pain Frequency 2) Change in Pain Intensity	1) Positive 2) Positive
Amitriptyline Satur, 2005	Rome II criteria for FAP, FD, IBS	4 Weeks	12.7 years	1) Satisfactory Relief 2) Satisfaction with Treatment	1) Negative 2) Negative
Famotidine Satur, 2005	Ajley's criteria for IBS	6 Weeks	10.5 years	1) Abdominal Pain Score 2) Global Assessment	1) Negative 2) Positive
Pilothen Syrup Satur, 2005	Abdominal Migraine for at least six months	16 weeks	Not Provided	1) Days of Abdominal Pain 2) Index of Severity	1) Positive 2) Positive
Citalopram Muller, 2014	Rome III criteria for FAP	4 weeks	10.4 years	Change in Pain Intensity	Negative

## Why we can't believe all clinical trials?

Patient A:

15 y/o with 22 month history of chronic abdominal pain  
 -pain daily  
 -nausea  
 -has missed 28 days of school this year

Patient B:  
 15 y/o with 22 month history of chronic abdominal pain  
 -pain 4 days per week  
 -pain 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**

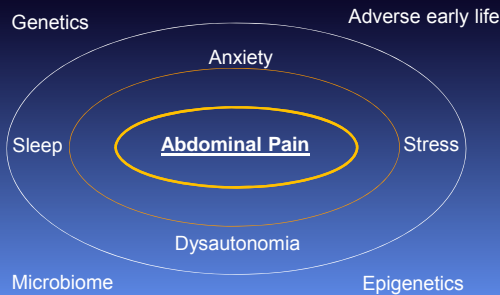
## What Animal Are We studying?



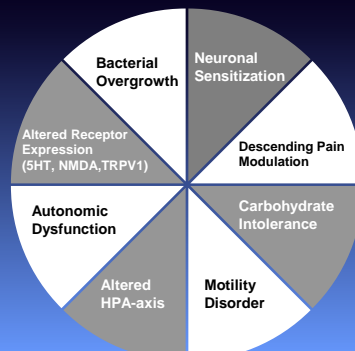
## It's Not Just Pain We Have to Address

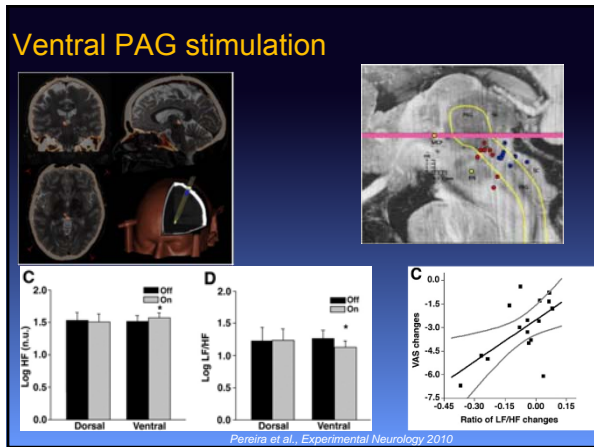
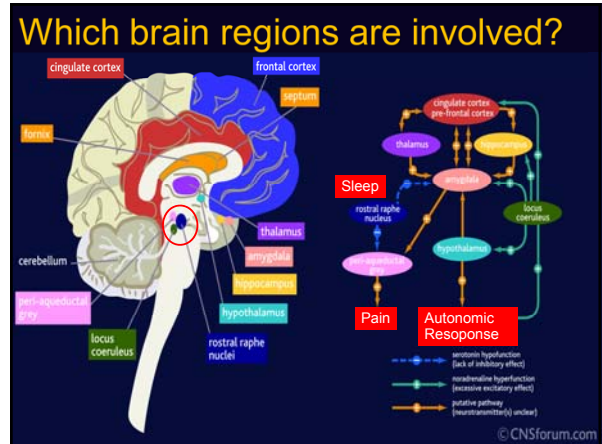
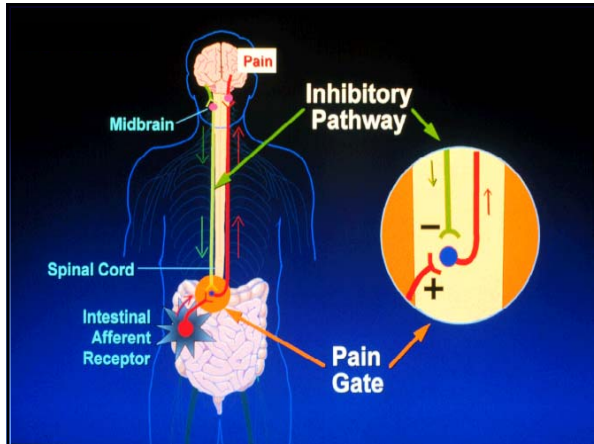
- Bloating
- Headaches
- Fatigue
- Sleep disruption
- Nausea
- Dizziness with postural changes
- Early satiety
- Anxiety

## Can we link it all together ?



## Proposed Underlying Mechanisms for Chronic Functional Abdominal Pain



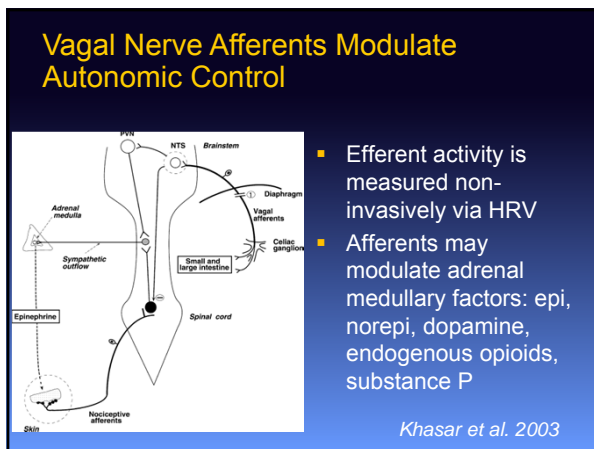


### Gut Vagal Afferents Differentially Modulate Innate Anxiety and Learned Fear

Klarer M, Arnold M, Günther L, Winter C, Langhans W, Meyer U. *J Neurosci.* 2014

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

C.H. Knowles, Q. Aziz. *PAIN.* 2009

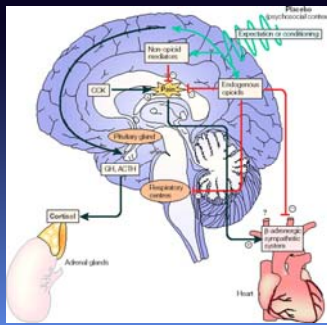


### Psychological Therapy

- Parent Attention Versus Distraction: impact on symptom complaints by children with and without chronic functional abdominal pain.**  
*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.**  
*Robins PM et al., 2005*

## Responding to Placebo Does Not Make You "Crazy"

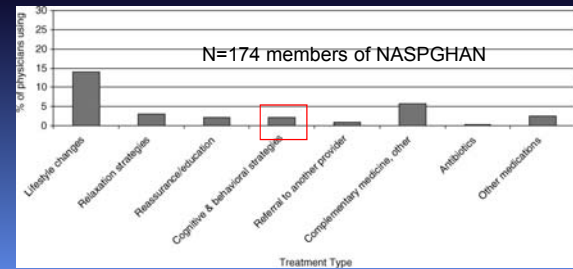
- Perform distracting tasks activate PAG, parts of ACC, and orbitofrontal cortex
- Placebo activates endogenous opioids and induces mild respiratory depression and decreases adrenergic activity



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

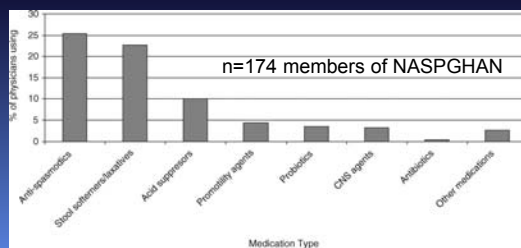
The Journal of Neuroscience  
©2005 by Society for Neuroscience

## Treatment used for FAP



Schurman et al., J Pediatr Gastroenterol Nutr. 2010

## Medication for Functional Abdominal Pain in Children



Schurman et al., J Pediatr Gastroenterol Nutr. 2010

## Pharmacological Treatment Options

### Mild Pain (no disability)

- Peppermint oil
- Iberogast
- Melatonin
- Probiotics
- Acid suppression

### Pain (with disability)

- TCAs (amitriptyline)
- SSRIs (citalopram)
- Gabapentin
- Antispasmodics (hyoscyamine, dicyclomine)
- Cyproheptadine
- Rifaximin

### 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?*

## 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

Bahar RJ et al., J Pediatr. 2008

**Multicenter, Randomized, Placebo-Controlled Trial of Amitriptyline in Children With Functional Gastrointestinal Disorders**

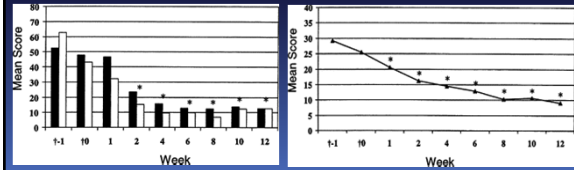
MIGUEL SAPS,\* NADER YOUSSEF,† ADRIAN MIRANDA,§ SAMUEL NURKO,‡ PAUL HYMAN,§ JOSE COCJIN,\* and CARLO DILLORENZO\*

- 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**

- 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:

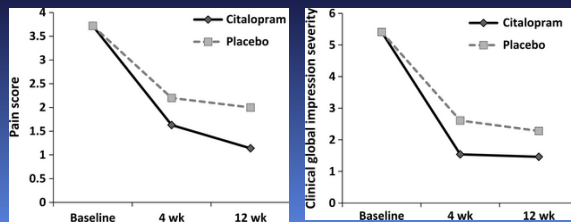
- not placebo controlled or blinded
- small group size (n=25)

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**

No Data in Children

- 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

Lee KJ, Kim JH, Cho SW. Aliment Pharmacol Ther. 2005

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

Collins BS, Lin HC. J Pediatr Gastroenterol Nutr. 2011

- 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**

Sadeghian M, Farahmand F, Fallahi GH, Abbasi A. Minerva Pediatr. 2008

- 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

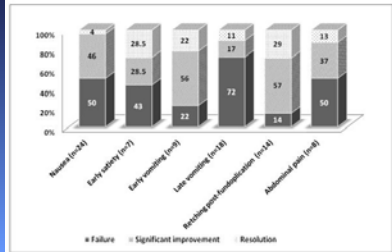
Weight gain, somnolence, irritability

### Safety and Efficacy of Cyproheptadine for Treating Dyspeptic Symptoms in Children

Rodriguez L, Diaz J, Nurko S. J Pediatr. 2013

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



-Barnes et al., 2008

### Melatonin Improves Pain and Decreases Activity of Spinal Neurons

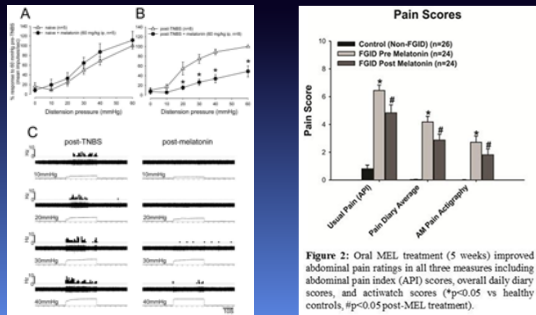


Figure 2: Oral MEL treatment (5 weeks) improved abdominal pain ratings in all three measures including abdominal pain index (API) scores, overall daily diary scores, and actiwatch scores (\*p<0.05 vs healthy controls, \*\*p<0.05 post-MEL treatment).

Mickle et al., Pain. 2010

### Melatonin

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

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

#### Therapeutic effect of melatonin in patients with functional dyspepsia.

Klupińska G, Poplawski T, Drzewoski J, Harasiuk A, Reiter RJ, Błasiak J, Chojnacki J

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

Chojnacki C, Walecka-Kapica E, Lokiec K, Pawłowicz M, Winczyk K, Chojnacki J, Klupińska G.

### (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

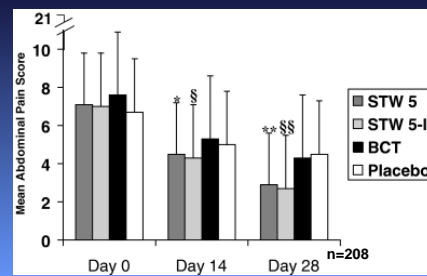
#### Side effects

Abdominal cramps, diarrhea, nausea, dizziness



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

Madisch A, Holtmann G, Plein K, Hotz J. Aliment Pharmacol Ther. 2004



**Enteric-coated, pH-dependent Peppermint Oil Capsules for the Treatment of Irritable Bowel Syndrome in Children.**

Kline RM, Kline JJ, Di Palma J, Barbero GJ.

- 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)

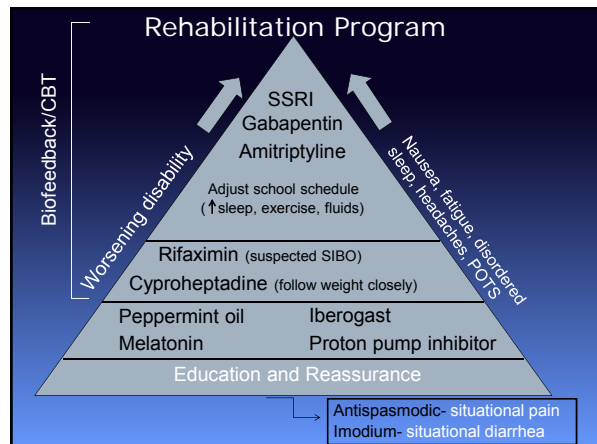
Dose

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

Side Effects

Heartburn, headache, flushing

*Kline et al., J Pediatr. 2001*



**Role of Exercise in Pain Control**

Rat model:

- Exercise increased  $\beta$ -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

*Stagg, NJ et al. Anesthesiology 2011*

*Johannesson et al., Am J Gastroenterol 2011*

**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