

## THE OVERLAP BETWEEN INFLAMMATORY BOWEL DISEASE AND FUNCTIONAL GASTROINTESTINAL DISORDERS: CHALLENGES AND TREATMENT IMPLICATIONS

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## Weekly Prevalence of Symptoms USA vs. Colombia

	Colombia n=285	USA (historical data) n=237	Significance
<small>Saps M, et al. J Pediatr. 2009;154:322-6.</small>			
<b>Gastrointestinal Symptoms</b>			
<b>Abdominal Pain</b>	36%	36%	NS
<b>Nauseas</b>	25%	23%	NS
<b>Constipation</b>	11%	8%	NS
<b>Diarrhea</b>	8%	9%	NS
<b>Vomiting</b>	7%	7%	NS
<b>Non- Gastrointestinal Symptoms</b>			
<b>Headaches</b>	31%	42%	<0.01
<b>Pain Arms Legs</b>	39%	30%	NS
<b>Chest Pain</b>	25%	15%	0.02

Saps M, et al. NASPGHAN 2011

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## MOST CHILDREN CONSULTING FOR ABDOMINAL PAIN DO NOT HAVE AN ORGANIC CAUSE TO EXPLAIN THEIR PAIN

10% of children miss school for abdominal pain

Children with abdominal pain have worse quality of life and disabilities

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

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## Sensation

Inflammation may lead to a cascade of cellular and nervous mechanisms may activate the nociceptive system independently of any mechanical changes.

Ulcerative colitis- inflammation lowers pain threshold to rectal distension

Chang L, et al. Gut 2000; 47: 497-505.



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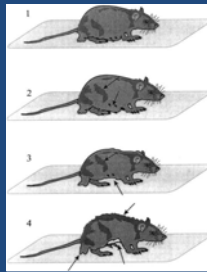
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## Colonic irritation in rats leads to visceral hypersensitivity



Al-Chaer ED, et al. Gastroenterology. 2000;119:1276-85



Abdominal Withdrawal Response with Colorectal Distension

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## Gastrointestinal Transit Sitz-Markers

### Active Colitis

- Gastric emptying- similar
- Mouth-to-caecum transit - slower
- Rectosigmoid- rapid transit

### Quiescent colitis

- Colonic distribution of markers was normal

Rao SS et al. Scand J Gastroenterol Suppl. 1990;172:22-8

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### Some IBD patients in clinical remission continue experiencing symptoms of pain despite resolving inflammation

- 30–50% of adult IBD patients in clinical remission (no inflammation) experience abdominal pain
- Up to one-sixth of IBD patients are chronically treated with opioids

Cross RK, et al. Am J Gastroenterol. 2005; 100:2225–2229.  
Edwards JT, et al. J Gastroenterol Hepatol. 2001; 16:1235–1238.  
Lichtenstein GR, et al. Clin Gastroenterol Hepatol. 2006; 4:621–630

- IBS-like symptoms among IBD patients in remission - 31.5% (UC), 41.7% (CD)

Minderhoud Im et al Dig Dis Sci. 2004;49:469-74.

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Prevalence of IBS-like symptoms among children with IBD  
CD 6%  
UC 14%

Dieren K, et al. DDW 2015

13% of children with IBD and abdominal pain have a functional disease

Zimmerman LA, et al. Inflamm Bowel Dis. 2013;19:826-31.



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### Overlap of functional abdominal pain in pediatric Crohn's disease

Zimmerman LA, et al. Inflamm Bowel Dis. 2013;19:826-31.

- Prevalence of FAP in children with inactive IBD is lower than adults and closer to the prevalence of functional disorders in general population of children
- Abdominal pain predominant-functional gastrointestinal disorders - 11.8%

Saps M, et al. J Pediatr. 2014;164:542-5.

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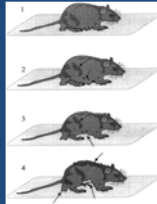
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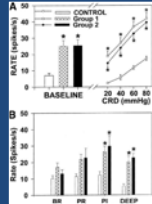
## Colonic irritation in neonatal rats, leads to chronic visceral hypersensitivity, associated with central neuronal sensitization in the absence of peripheric pathology



Al-Chaer ED, et al. Gastroenterology. 2000;119:1276-85



Abdominal Withdrawal Response



Colorectal Distension

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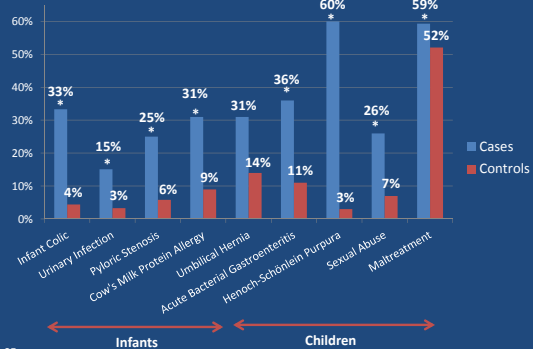
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## Early Life Events as Predictors of Pediatric Chronic Abdominal Pain



\* p<0.05

Infants Children

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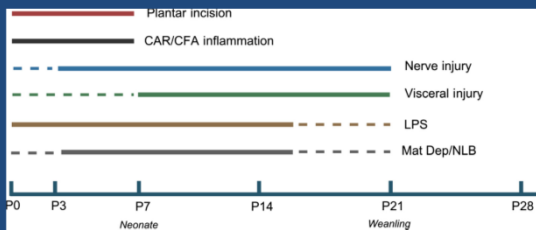
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## Critical periods for neonatal insults to cause long-term changes to pain and somatosensation (rodents)



Schwaller F, et al. Eur J Neurosci. 2014;39(3):344-52

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## Sensation

Chang L, et al. Gut 2000; 47: 497-505.

- Repetitive sigmoid stimulation - UC no fall in threshold
- IBS- Repetitive sigmoid stimulation reduced threshold for pain and falls even further
- **Chronic inflammation alone does not lead to visceral hypersensitivity**
- **Visceral hypersensitivity depends not only on peripheral input but also on descending influences (facilitatory and inhibitory)**

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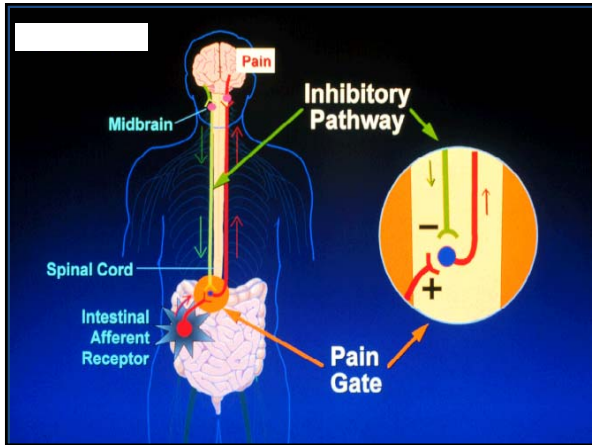
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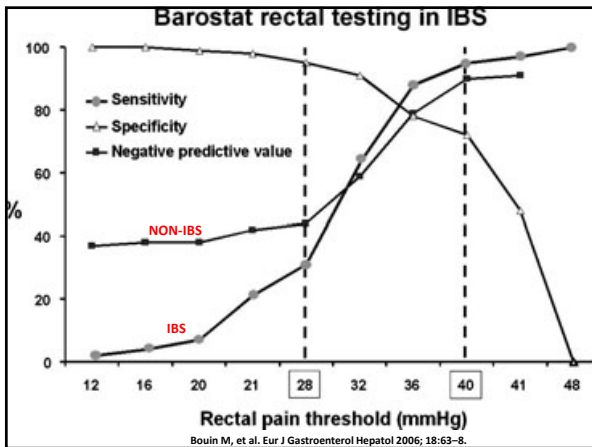
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## Some IBD patients in clinical remission continue experiencing symptoms of pain despite resolving inflammation

- Sensory pathways sensitize during inflammation, leading to persistent changes in afferent neurons and central nervous system pain processing.
- Pain processing and activation of sensory pathways is modulated by arousal, emotion, and cognitive factors.

Bielefeldt K, et al. Inflamm Bowel Disease 2009;15:778-88.

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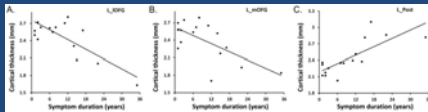
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## Differences in thickness between patients with chronic gut inflammation, functional GI disorders and healthy

Hong JY, et al. 2014;9(1):e84564.

- UC and IBS- lower cortical thickness in insula (different regions)
- UC- reduction certain areas (chronic inflammation driven afferent input)



Correlation Between Cortical Thickness and UC Symptom Duration

- Changes in somatosensory cortex in UC and IBS but degree did not correspond to pain reports (UC more changes and less pain than IBS)

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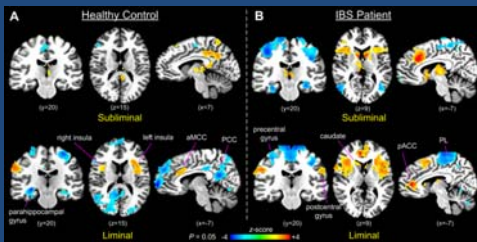
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## Rectal Distension Induced Activations

Sood M et al. NASPGHAN 2014



IBS patients demonstrated significantly increased activation in:  
 Anterior cingulate  
 Insula  
 Frontal cortex  
 Deactivation in sensory and motor areas

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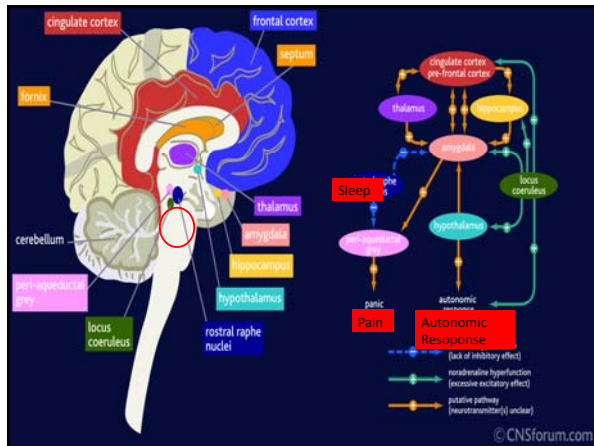
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### Health Quality of Life

- In IBD and IBS, psychological distress has a stronger direct effect on HRQOL than GI symptoms
- Psychological distress is less dependent on GI symptom severity in IBS compared with IBD

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### Persistent pain despite clinical remission

Biopsychosocial problem-  
Comorbidities including anxiety and depression in IBD patients have central modulating effects

Bielefeldt K, et al. Inflamm Bowel Disease 2009;15:778-88.

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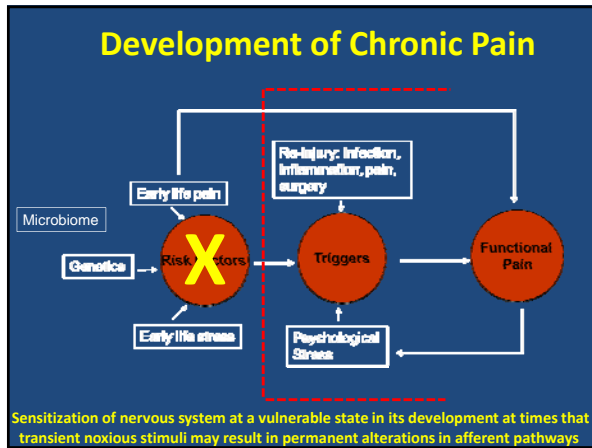
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**IBS and IBD patients have negative correlations between:**

- 1- Psychological symptoms and HRQOL
- 2- GI symptoms and HRQOL

**Difference between IBS and IBD**

- Greater association between GI symptoms and psychological distress in IBD
- Psychological distress less dependent on severity of GI symptoms in IBS than IBD

Psychological distress is related to worsening GI symptoms in IBD patients and therefore may improve with relief of GI symptoms

Naliboff BD, et al. Am J Gastroenterol. 2012;107:451-9.

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	Medical Therapy		Hypnotherapy	
	Before	After	Before	After
Rectal sensitivity scores	15 mm Hg	19 mm Hg (P=0.09)	17 mm Hg	22.5 mm Hg (P=0.09)
Patients with rectal hypersensitivity (N)	6/20	4/20 (P=0.67)	6/18	0/18 (P=0.04)

- **Treatment outcomes:** Although rectal hypersensitivity improved in hypnosis, rectal hypersensitivity did not correlate with outcome
- **Conclusion:** Clinical success with hypnotherapy not explained by improvement in rectal sensitivity.



Vlieger AM, et al. Am J Gastroenterol. 2010;105:213-8

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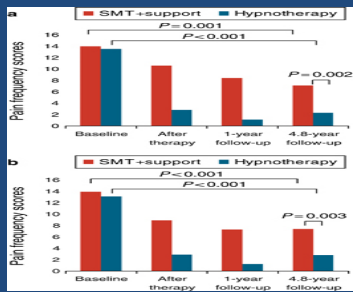
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## Hypnosis



Am J Gastroenterol 2012; 107:627-631

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- State of deep relaxation
- Focused attention
- Teach patients to control symptoms and physiological functions not easily accessible to conscious manipulation

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## Ulcerative Colitis Hypnotherapy Trial

- Prevention of relapse
- Randomized clinical trial comparing 7 sessions of standardized gut-directed hypnotherapy (n=19) versus active attention (n=17)
- Improvement in the IBDQ bowel health subscale with the hypnosis at 20 weeks (p = .05).
- Hypnosis reported more improvement in physical quality of life over time at both posttreatment (p = .04) and 20 weeks (p = .03).

Keefer L, et al. Biol Res Nurs. 2012;14:71-7.

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## Predicting relapse in Crohn's disease

Bitton A, et al. Gut. 2008; 57:1386-92.

- Temporal relationship between psychological distress and acute stressors
- Stressors- Worsening of IBD symptoms and subsequently a disease flare.
- Patients under low stress and low on avoidance coping (social diversion or distraction) are less likely to relapse.

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## IBD – Anxiety- Depression

- 36 adolescents with IBD (ages 12-17)
- Clinical levels of anxiety (22%)
- Depressive symptoms (30%)
- Regression analyses - IBD-specific anxiety significantly associated with greater utilization of medical services and worsened psychosocial functioning.

Reigada L, et al. J Spec Pediatr Nurs. 2011;16:207-15

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## Adolescents with IBD

- Adolescents with IBD (n=50), healthy (n=42)
- Higher risk for psychosocial difficulties than healthy adolescents
- IBD more anxious or depressed symptoms ( $p < .05$ ) and social problems ( $p < .01$ )
- More adolescents with IBD (14%) - clinically significant social problems

Mackner LM, et al. J Pediatr Psychol. 2006;31:281-5.

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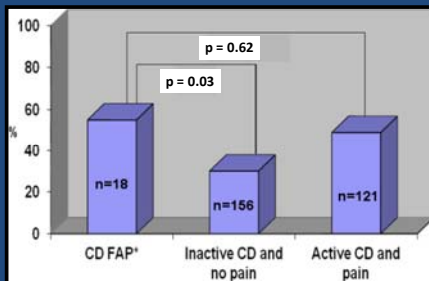
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## Children with CD and abdominal pain at risk of depression regardless of disease activity

Zimmerman LA, et al. Inflamm Bowel Dis. 2013;19:826-31.



Proportion of patients with Crohn's disease and functional abdominal pain with depressive symptoms compared to other Crohn's disease patients.

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## Parenting stress predicts depressive symptoms in adolescents with inflammatory bowel disease.

- Baseline parenting stress accounts for a significant amount of the variance in depressive symptoms at follow-up ( $P < 0.05$ ).
- **CONCLUSION:** Parenting stress impacts adolescent depressive symptoms in IBD. Identification of parenting stress and adolescent depression should occur early and possibly in the context of routine clinic visits.

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## Behavioral Self-Management Program

- Comprehensive program to address stress and improve coping for the management of IBD (8 weeks)
- Techniques for stress management, and increased self-efficacy - disease/medication knowledge, coping and medication adherence
- Incidence of flare within 12 months following behavioral intervention compared to natural history of flare incidence prior to program participation

	Before	After	Decrease	
Treatment	13.1%	6.1%	57%	p<.001
Control	10.2%	8.5%	18%	p=0.4

Keefer L, et al. Behav Res Ther. 2011;49:145-50.

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## IBD and anxiety

- 9 children/adolescents with IBD and anxiety
- CBT program at GI's office
- Pretreatment vs. post-treatment- 88% treatment responders, 50% no longer met criteria for their principal anxiety disorder
- Decreases in: anxiety, pain, disease severity

Reigada LC, et al. J Spec Pediatr Nurs. 2013;18:133-43

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## Primary and Secondary Prevention

Saps M, et al. Unpublished data

Abdominal Pain	Change
Prevalence	NS
Severity	p<.07
<b>Headaches</b>	
Prevalence	p=0.04
Severity	p<.001
<b>Functioning</b>	p<.001
Play	p<.03
Gymnastics	p<.001
Absenteeism	p<.03

Intervention group missed 1.3 less days of school control group (p=.01)

4% of children with abdominal pain seek medical attention

Saps M, et al. J Pediatr. 2009; 154:322-26.

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Abdominal Pain IBS

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### Psychological Risk Factors

5 Year Longitudinal Study: Children with persistent abdominal pain > anxiety, depression and negative life events and lower self worth

Mulvaney S, et al. J Am Acad Child Adolesc Psychiatry. 2006;45:737-44

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