Visceral Sensation & Pain

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Extreme Example?

- 48 year-old woman with idiopathic gastroparesis.
- Symptoms (nausea, vomiting and abdominal pain) started 3 years ago and progressively worsened. She has a weight loss of 15 kg with BMI of 17.
- She has failed dietary management and prokinetics.
- She is on Dilaudid 2 mg every 4 h for > 6 months.

The Pain

Her pain is

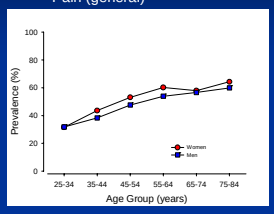
- epigastric
- constant, described as a severe ache
- non-radiating
- exacerbated by food intake
- only alleviated by centrally acting opioids.

Questions

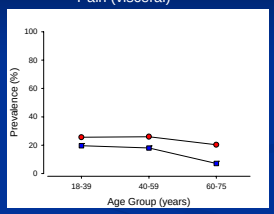
- How common is visceral pain?
- What is unique about visceral pain?
- How can we/should we treat visceral pain?

Pain Prevalence & Age

Pain (general)



Pain (visceral)



Pain prevalence increases with age.

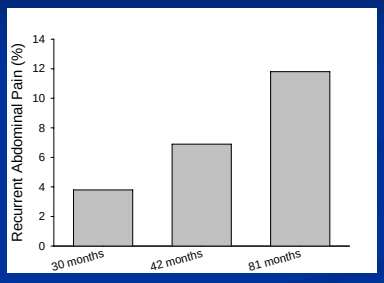
Abdominal pain is different:

Gender effect

Minor (no) age effect

Lancet, 354:1248-52, 1999 *Digestive Diseases & Sciences, 45:1166-71, 2000*

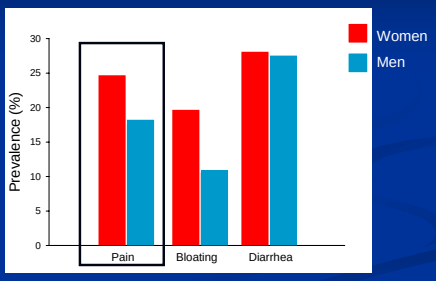
It Starts Early…



Female predominance
OR: 1.59 (1.39–1.82)

Pediatrics 116: 46-50, 2005

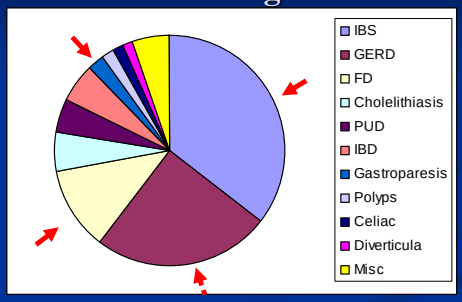
… And Continues On



Phone Survey of 2510 Adults

Digestive Diseases & Sciences. 45(6):1166-71, 2000

Pain as a Common Clinical Challenge



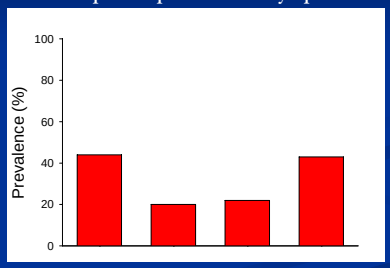
Prospective study of 568 outpatients.

Gut 53: 666-672, 2004

Chronic Gut Pain

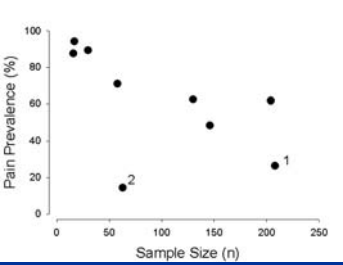
IBS & 'Dyspepsia'

Severe pain as predominant symptom



American Journal of Gastroenterology. 101: 124-32
Gastroenterology. 130:296-303
Aimentary Pharmacology & Therapeutics **20**, 339-345
European Journal of Gastroenterology & Hepatology. 16:995-1001

Back to the Case (Gastroparesis)



Pain is a prominent symptom in gastroparesis – an apparently well defined gastric motor disorder.

1 – 'dominant symptom'
2 – retrospective study

Karamanolis 2007
McCallum 1998
Parkmann 2002
Pasricha 1999
Silvers 1997
McCallum 1996

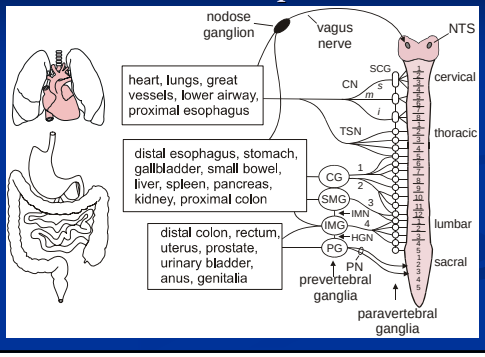
My Experience

- Female predominance (41/50 patients).
- 40/50 patients had at least some pain.
- 22 of 50 patients with gastroparesis listed pain as the dominant symptom.
- 14/50 patients used opioids at least once daily.

So…

- Visceral (abdominal) pain is common.
- The epidemiology of visceral pain appears distinct.
- Female predominance is important (we can speculate about reasons).

Blast from the Past
Structural Components



Gut Level Feelings
Some Basics

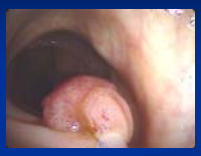
- We sense a lot.
- We feel very little.
- We weigh it heavily.

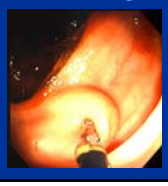
What Do We Feel?

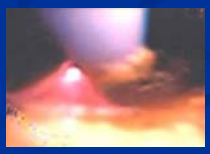
- Fullness, distension, bloating (*mechanical, stretch*)
- Cramps, spasm (*motility, tension*)
- Burning (*chemical/inflammation*)
- Nausea (*chemical & mechanical*)
- Ache (*inflammation*)

What We Do NOT Feel?

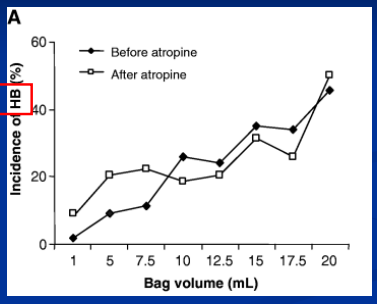
Cutting
Burning
Pinching







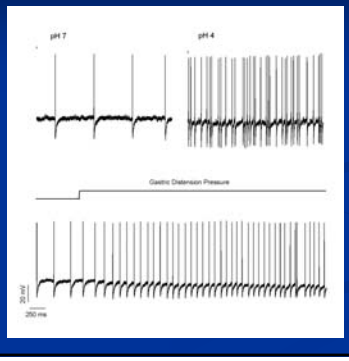
Can We Trust Our Senses?



Esophageal distension triggers heartburn!

Neurogastroenterol Motil 16: 721-728;2004

The Physiology Behind It

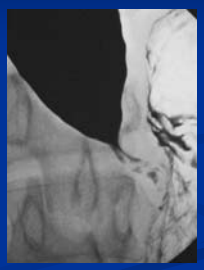


Recordings from a single gastric sensory neuron demonstrate responses to gastric acidification and distension (*polymodal*).

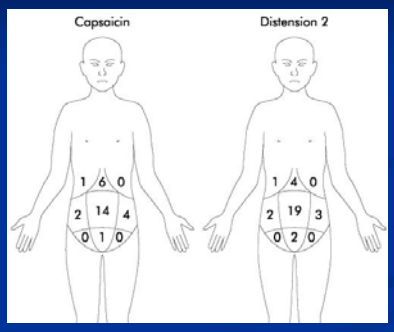
Remember nociceptors.

Clinical Correlates

- Heartburn is mostly – not always – due to acid reflux.
- It is often present and rarely the presenting symptom in achalasia.



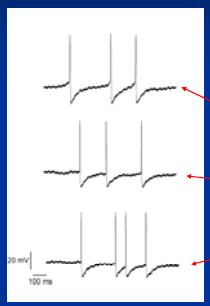
What About Location?

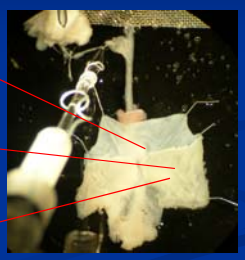


Site of discomfort in response to chemical or mechanical stimulation of the proximal jejunum in 29 volunteers.

Gut 53: 1109-1116, 2004

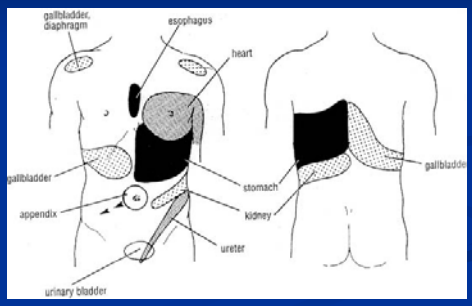
Reasons for Poor Accuracy





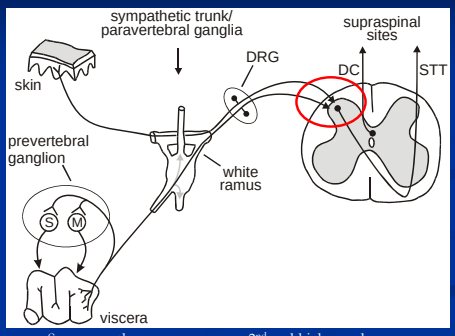
One neuron, many receptive fields.

Pain Referral



Yamada et al (ed.) Textbook of Gastroenterology, 2003

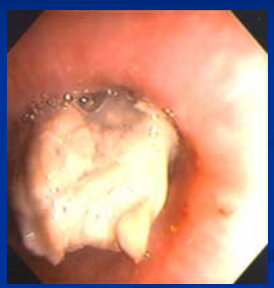
Basis of Pain Referral: Convergence



Sensory pathways converge on 2nd and higher order neurons.

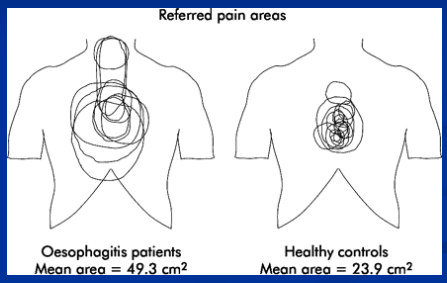
Clinical Correlate

Subjective location of bolus obstruction in the neck area despite distal esophageal problems.



Plasticity of Pain Referral

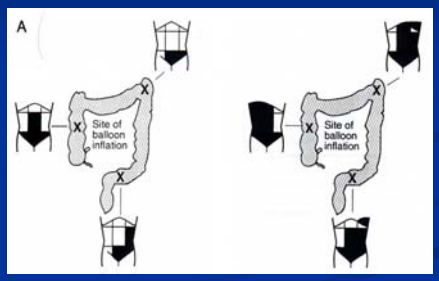
Sensation in response to balloon distension.



Gut: 55: 926-932;2006.

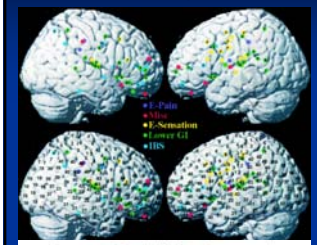
More on Clinical Correlates

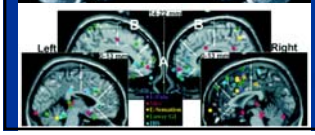
Control IBS



Mayer & Gebhart, Gastroenterology 1994

Feeling Pain Requires Brain





Sensory & motor cortex

Insula (anterior > posterior)

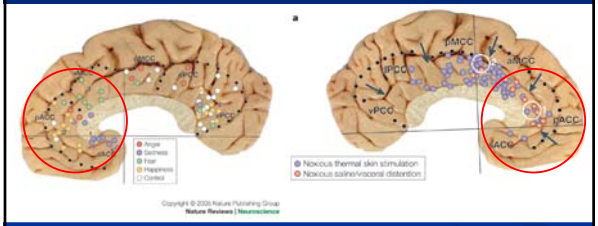
Anterior cingulate cortex

Prefrontal cortex

BASICALLY: MUCH IS IN MIDLINE STRUCTURES

American Journal of Gastroenterology 2003;98:12-20.

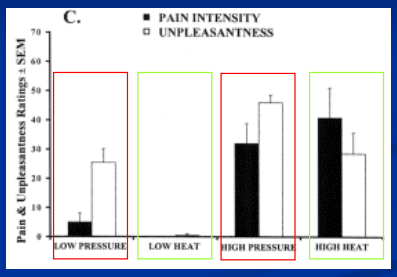
A Look at the Neighborhood



Emotion Sensation

Nature Reviews Neuroscience **6**: 533-544; 2005

Differential Impact



Visceral pain triggers stronger emotional response than somatic pain.

Pain 97: 235-246, 2002

Summary

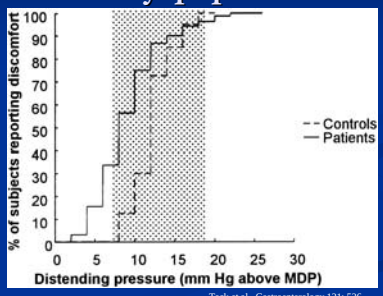
- Visceral Sensation and Pain have
  - a poor discriminatory value (spatial and modality)
  - a characteristic referral pattern
  - strong emotional & autonomic reactions
  - distinct triggers

Plasticity

Clinical Scenario

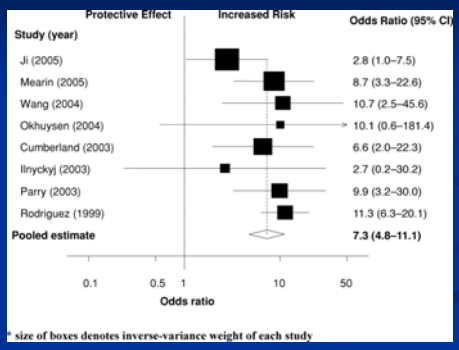
- 43 year-old woman with bloating, intermittent epigastric pain and postprandial fullness.
- Symptoms started 6 months ago after she ate pirogies and developed an acute gastroenteritis.
- **Physical examination, laboratory testing (even an endoscopy and gastric emptying study) were all normal.**

Sensation & Functional Dyspepsia



Tack et al., Gastroenterology 121: 526

Infection & Functional GI Disease



American Journal of Gastroenterology: 101: 1894-189

Role of Bugs

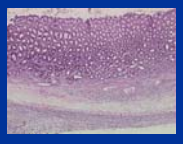
	Six Months (n = 748)		
	Odds Ratio	95% CI	p
	IBS vs. noncases		
Gender (M vs. F)	2.36	1.23–3.98	.01
Age	0.99	0.97–1.01	.11
Acute illness type (IM vs. CG)	2.42	1.18–4.94	.01
Anxiety	1.82	1.05–1.22	.03
Depression	1.39	0.90–1.07	.35
Intercept			<.001
	CFS vs. noncases		
Gender (M vs. F)	1.49	0.71–3.13	.29
Age	1.00	0.97–1.03	.94
Acute illness type (CG vs. IM)[a]	1.30	0.52–3.22	.58

What can science tell us?

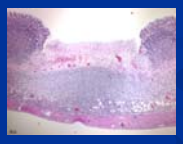
Psychosom Med 68: 463-469, 2006

Experimental Model

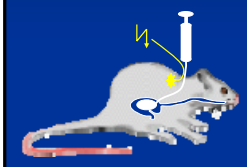
HAc-Injection

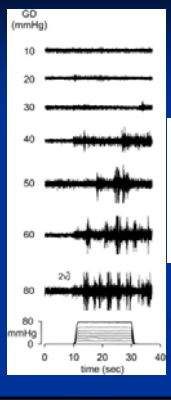


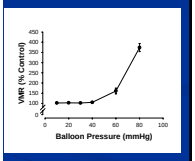
Luminal HAc



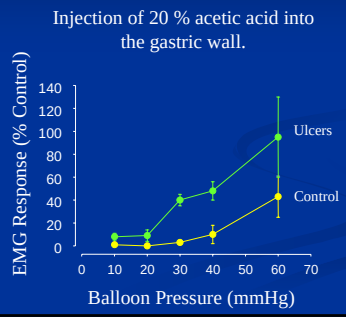
Behavioral Assay



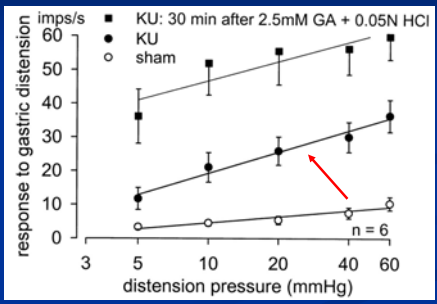




Mechanosensation & Ulcers

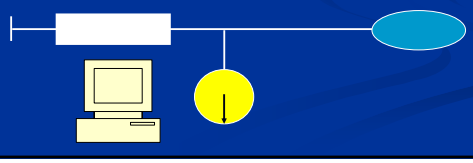


Ulcers & Peripheral Sensitization

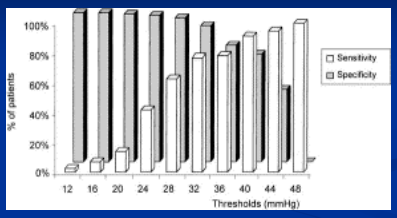


Can We Check This in Humans?

- Hollow organ distension
  - Volume (iso-volumetric)
  - Pressure (iso-baric)



Barostat-Patients

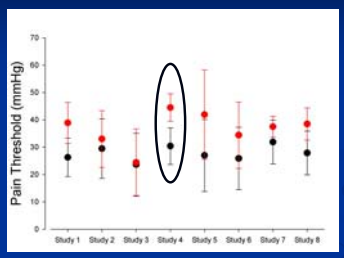


IBS (n = 86) and non-IBS (n = 103) subjects

Distension testing as biomarker?

Gastroenterology. 122(7):1771-7, 2002

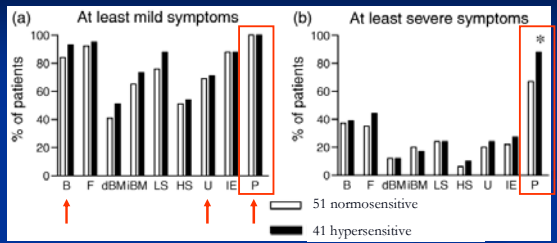
Distension as Biomarker 1



Wrong test?

One of many mechanisms?

Distension as Biomarker 2



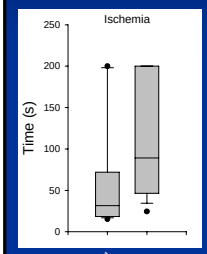
B - bloating; F - flatulence; dBM - decreased bowel movements; iBM - increased bowel movements; LS - loose stools; HS - hard stools; U - urgency; IE - incomplete evacuation; P - pain

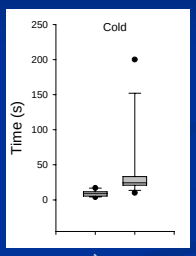
Sensory testing detects abnormalities in a subgroup.

Poor correlation between symptoms and test results.

Alimentary Pharmacology & Therapeutics **22** (2), 157-164

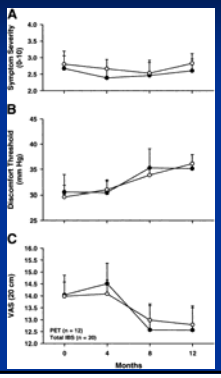
Problems with Biomarkers & Pain





Most pain measures have a significant inter-individual variability.

Problems with Biomarkers & Pain



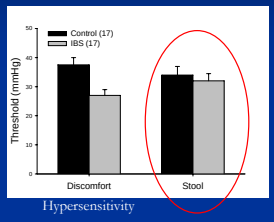
Stable symptoms

Reflection of stress and vigilance rather than hypersensitivity.

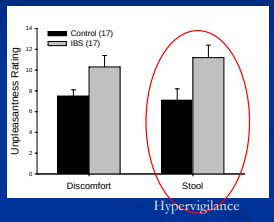
TEST

Gastroenterology: 131(2): 352-365;2006

Hypersensitivity vs. Hypervigilance



Hypersensitivity



Hypervigilance

Sensation is similar, yet interpretation differs for some gut-related stimuli.

Gut 41: 505-512, 1997

So…

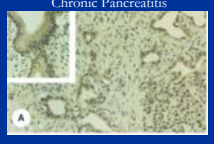
- Inflammation (and other factors) can sensitize visceral afferents.
- Peripheral sensitization contributes to the development of hyperalgesia.
- Experimental pain measurement in humans is problematic
  - poorly correlates with clinical presentation
  - reflects central contributions (focus/vigilance)

Peripheral Sensitization
Translational Concepts

NGF & Chronic Pancreatitis

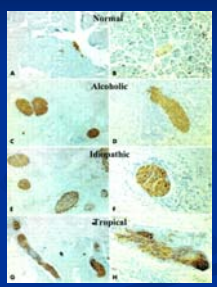
Control

Chronic Pancreatitis



50 % increase in NGF mRNA

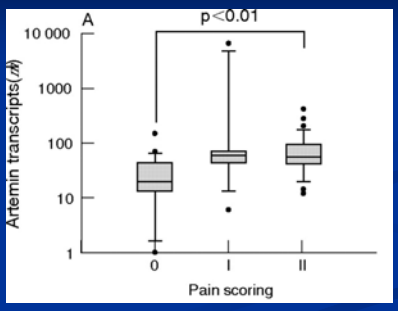
Annals of Surgery: 230: 615-24;1999



Big nerve bundles are seen in all forms of CP.

Gut 2002;**50**:682-686

Similar Pattern with Artemin



Gut 2007;**56**:534-544

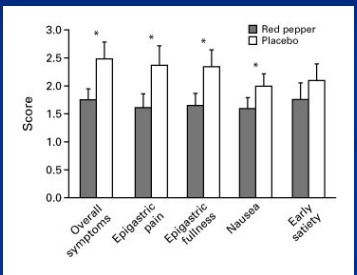
Structural & Functional Plasticity

Increase in nerve density and TRPV1

- esophagitis and non-erosive reflux disease
- ulcerative proctitis
- IBS
- 'rectal' urgency
- interstitial cystitis

Common denominator: ***pain***

Implications: 'Burn It Down'

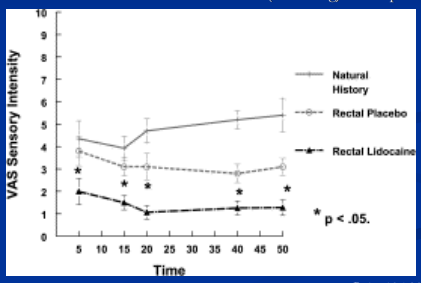


Hot pepper (0.7 g capsaicin) and functional dyspepsia.

NEJM 346:947-948

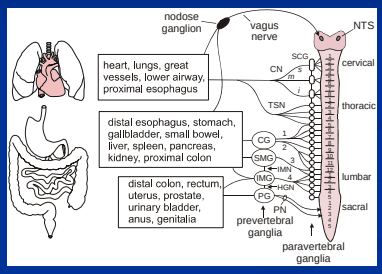
Remember Sodium Currents?

Effect of rectal lidocaine on rectal distension (35 mmHg) in IBS patients



Pain. 105:223-30, 2003

Regional Blocks: Conceptual Issues

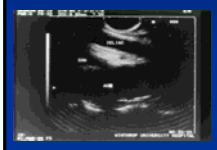


Complexity of visceral peripheral innervation.

Regional Blocks: Experience

Pancreatitis

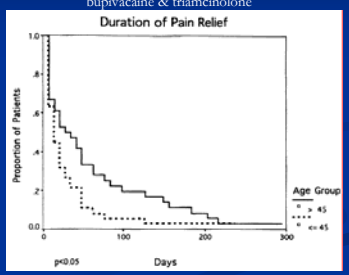
bupivacaine & triamcinolone



Difficult to get to.

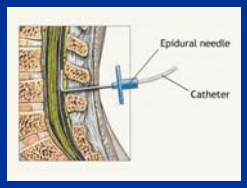
Celiac plexus vs. splanchnics

Response: ~ 50 %



Am J Gastroenterol: 96: 409-416;2001

The Brain Again as "Problem"



Chronic pancreatitis & pain (n=23)

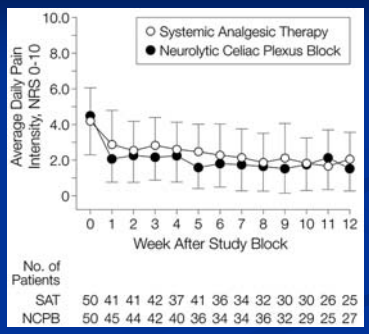
Neuroaxial block

Pain (n=14)

No pain (n=9)

American Journal of Gastroenterology 96: 431-436, 2001

A Different 'Clientele'

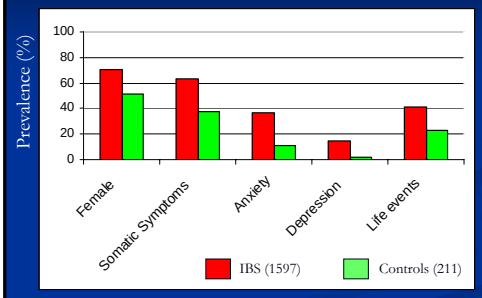


JAMA: 291(9): 1092-1099;2004

So…

- Peripheral mechanisms contribute to human pain disorders.
- Therapies targeting peripheral structures (channels, receptors, nerves) have a role in visceral pain syndromes.
- Again, the brain confounds.

Epidemiologic Clues

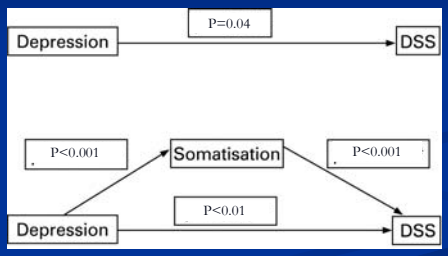


Int. J. Epidemiol. 35: 468-476, 2006

Back to Gastroparesis

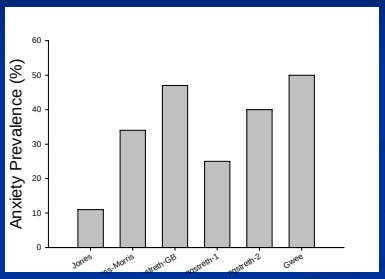
- Significant anxiety/depression: 72%
- Depression accounts for at least 20% of the perceived impairment of QoL.

Functional Dyspepsia



Gut 2008;57:1666-1673

IBS - Brain as Fertile Ground



Alimentary Pharmacology & Therapeutics **24** (5), 879-886

Psychosomatic Medicine. 68(3):463-9, 2006

Alimentary Pharmacology & Therapeutics **15** (7), 959-964

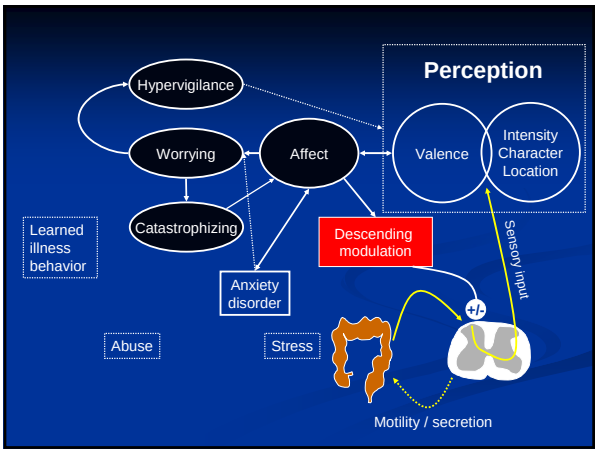
The Lancet 347: 150-153, 1996

Initiation & Perpetuation

	Six Months (n = 748)		
	Odds Ratio	95% CI	p
	IBS vs. noncases		
Gender (M vs. F)	2.36	1.23–3.98	.01
Age	0.99	0.97–1.01	.11
Acute illness type (IM vs. CG)	2.42	1.18–4.94	.01
Anxiety	1.82	1.05–1.22	.03
Depression	1.39	0.90–1.07	.35
Intercept			<.001
	CFS vs. noncases		
Gender (M vs. F)	1.49	0.71–3.13	.29
Age	1.00	0.97–1.03	.94
Acute illness type (CG vs. IM)[a]	1.30	0.52–3.22	.58
Anxiety	2.58	1.24–5.35	.01
Depression	3.95	1.87–8.36	<.001
Intercept			<.001

IM = infectious mononucleosis; CG = *Campylobacter* gastroenteritis.
[a] Odds ratios have been inverted to reflect the relative risk for CG vs. IM as opposed to IM vs. CG.

Psychosom Med 68: 463-469, 2006

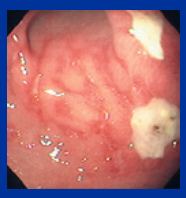


Back to the Patient - Treatment

- NSAID (peripheral)
- Opioids (central)
- TCA/SSRI/duloxetine (central)
- Miscellaneous

Pick your poison (or 'placebo')

NSAID



Perhaps not so good for the gut.

-Dyspepsia 18-50 %

-PUD 6-47%

No systematic studies.

Dig Dis Sci 53: 2059

Dig. Diseases 24: 189

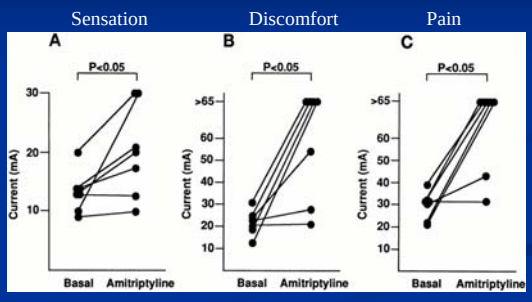
Clin & Exp. Rheumatol 20: 35

Back to the Patient

- NSAID (peripheral)
- Opioids (central)
- TCA/SSRI/duloxetine (central)
- Miscellaneous

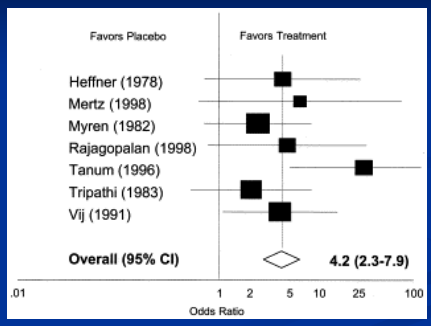
Therapeutic Implications?

Antidepressants – Acute Effects in Controls



Gorelick et al., AJP 275: G460

A Hint for the Clinic (IBS)

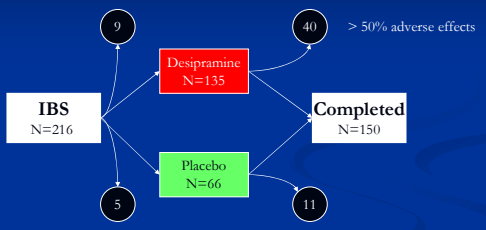


Cochrane analysis:

Insufficient evidence of efficacy.

Am J Med 2000; 108: 65

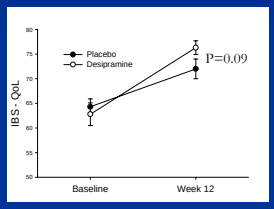
Beyond Meta-Analysis (IBS)



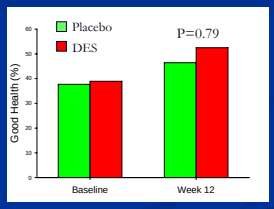
Gastroenterology 2003;125:19-31

Overall Effects

Composite Score

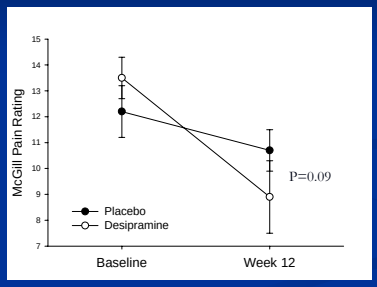


Global Rating



Gastroenterology 2003;125:19-31

What About Pain?



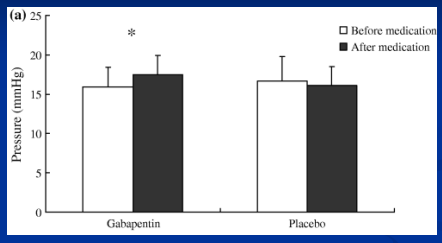
Things look better if you analyze *per protocol*. So, we can still claim a rationale.

Gastroenterology 2003;125:19-31

Back to the Patient

- NSAID (peripheral)
- Opioids (central)
- TCA/SSRI/duloxetine (central)
- Miscellaneous

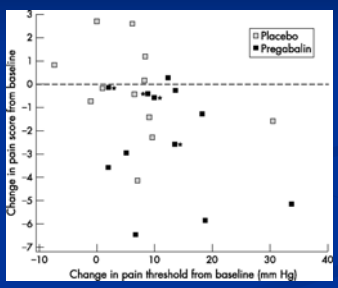
α2δ as the Answer?



Gabapentin acutely reduced pain threshold in response to rectal distension.

Aliment Pharmacol Ther 2005;22:981-988

However…



No significant change in pain score after 2 weeks of pregabalin.

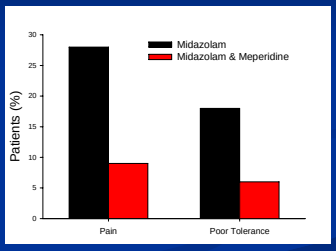
Gut 2007;56:1218-1225

Back to the Patient

- NSAID (peripheral)
- Opioids (central)
- TCA/SSRI/duloxetine (central)
- Miscellaneous

Opioids & Visceral Pain

- Anecdotal evidence
  - ER practice
  - Colonoscopy



Gastrointest Endosc. 2003; 57:329

Opioids & Benign Disease

- Prevalence
  - 3-66% of patients with chronic lower back pain
  - 28% in gastroparesis; 7-15% in IBD
- Long-term efficacy
  - Limited data from poor trials
  - Improvement of pain control (QoL) but not function
- Addiction
  - Deviation from prescribed dosage up to 25%

J Opioid Management 4: 153; J Pain 8:175; Ann Int Med 146: 116

Consequences of Chronic Opioids

- Habituation
  - No clear evidence of dose escalation in chronic treatment trials.
- Dependence
- Addiction
- Opioid-Induced Hyperalgesia
  - Controversial (observed with addicts/dose escalation)

Med Clin North Am 2007;91:199-211

Opioids and GI Disease

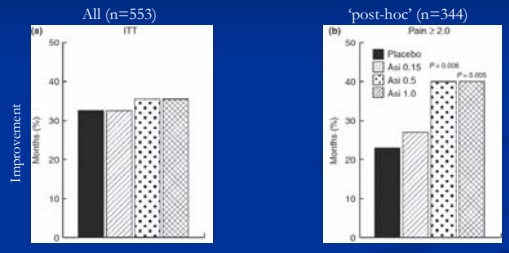
- Nausea & vomiting: 15-40% (typically transient)
- Constipation: 15% (persistent)
- Delay in GI transit (incl. gastric emptying).

So, they do work, but come with 'baggage' and concerns.

What About κ-Agonists?

All (n=553)

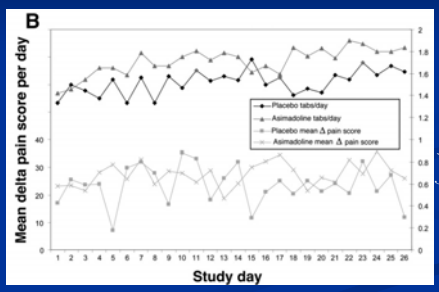
'post-hoc' (n=344)



Additional 'post hoc' info: worked best in IBS-D; decreased bowel frequency

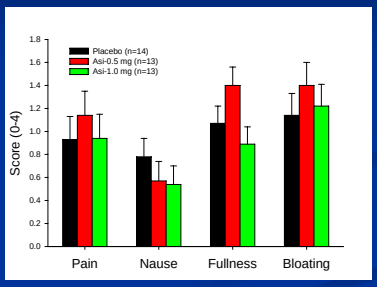
Aliment Pharmacol Ther 2008;28:239-249

No Acute Analgesic Effect in IBS



Clinical Gastroenterology and Hepatology 2007;5:1268-1275

Asimadoline in Functional Dyspepsia

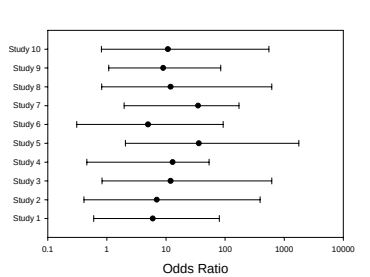


Aliment Pharmacol Ther 2008;27:1122-1131

Focus on the Brain

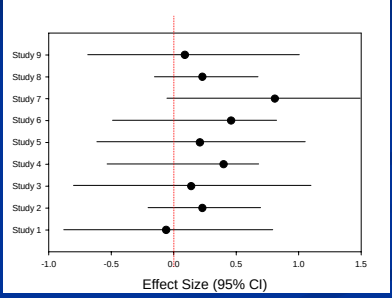
- Hypnotherapy
- Cognitive behavioral therapy
- Psychotherapy

Psychological Therapy
Global Improvement vs. Control



J Consult Clin Psychol 2004;72:1100-1113

What About Pain?



J Consult Clin Psychol 2004;72:1100-1113

The Bottom Line

- Visceral pain is different (epidemiology, triggers, referral, affect).
- We are still missing the 'golden grail' of pain management.
- Analgesic medications often cause adverse effects on the gut (but they do work).