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.

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?

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**Pain Prevalence & Age**

Pain prevalence increases with age.

Abdominal pain is different:

- Gender effect
- Minor (no) age effect


*Digestive Diseases & Sciences.* 45:1166-71, 2000

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**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. 95:124-32
Gastroenterology. 116:296-301
Gastroenterology & Therapeutics. 20:339-345
European Journal of Gastroenterology & Hepatology. 16:995-1001

Gastroenterology. 130:296-303
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).
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!

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.

Reasons for Poor Accuracy

One neuron, many receptive fields.
**Pain Referral**

**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.

More on Clinical Correlates

Control  IBS

Feeling Pain Requires Brain

Sensory & motor cortex
Insula (anterior > posterior)
Anterior cingulate cortex
Prefrontal cortex

BASICALLY: MUCH IS IN MIDLINE STRUCTURES
Visceral pain triggers stronger emotional response than somatic pain.

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 pierogies and developed an acute gastroenteritis.
- Physical examination, laboratory testing (even an endoscopy and gastric emptying study) were all normal.

Sensation & Functional Dyspepsia

- Graph showing distending pressure (mm Hg above MDP) vs. % of subjects reporting discomfort.
- Controls vs. Patients indicated.

Infection & Functional GI Disease

- Table showing studies, reported effect, increased risk, odd ratios, and 95% CI.
- Odd ratios range from 2.0 to 11.3 with 95% CIs also provided.

Tack et al., Gastroenterology 121: 526

American Journal of Gastroenterology: 101: 1894-189
Role of Bugs

Sex Identity (n = 748)

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M vs. F)</td>
<td>3.36</td>
<td>0.53-1.84</td>
</tr>
<tr>
<td>Age</td>
<td>2.01</td>
<td>1.88-1.96</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.82</td>
<td>1.59-2.12</td>
</tr>
<tr>
<td>Depression</td>
<td>1.39</td>
<td>0.96-1.67</td>
</tr>
<tr>
<td>Intercept</td>
<td>1.00</td>
<td>0.96-1.05</td>
</tr>
</tbody>
</table>


What can science tell us?

Experimental Model

HAc-Injection  Luminal HAc

Behavioral Assay

[Graphs and images related to behavioral assays]
Mechanosensation & Ulcers

Injection of 20% acetic acid into the gastric wall.

EMG Response (% Control)

Balloon Pressure (mmHg)

- Ulcers
- Control

Ulcers & Peripheral Sensitization

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

Can We Check This in Humans?
Barostat-Patients

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

Distension testing as biomarker?

Distension as Biomarker 1

Wrong test?
One of many mechanisms?

Distension as Biomarker 2

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.

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

50% increase in NGF mRNA

Big nerve bundles are seen in all forms of CP.
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 capsicin) and functional dyspepsia.
Remember Sodium Currents?

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

Regional Blocks: Conceptual Issues

Complexity of visceral peripheral innervation.

Regional Blocks: Experience

Pancreatitis

Difficult to get to.
Celiac plexus vs. splanchnics
Response: ~ 50%
The Brain Again as “Problem”

Chronic pancreatitis & pain (n=23)

Neuroaxial block

Pain (n=14)

No pain (n=9)


A Different ‘Clientele’

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.
Central Mechanisms

Epidemiologic Clues

Prevalence (%)

Female
Social Symptoms
Anxiety
Depression
Life events

IBS (1597) Controls (211)

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.
Back to the Patient - Treatment

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

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

Sensation Discomfort Pain

A Hint for the Clinic (IBS)

<table>
<thead>
<tr>
<th>Favorable Placebo</th>
<th>Favorable Treatment</th>
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<tbody>
<tr>
<td>Heffner (1978)</td>
<td></td>
</tr>
<tr>
<td>Meitz (1986)</td>
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<tr>
<td>Myers (1982)</td>
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<td>Rajeepalan (1986)</td>
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<td>Tanam (1996)</td>
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<td>Tripathi (1983)</td>
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<tr>
<td>Voj (1981)</td>
<td></td>
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</tbody>
</table>

Overall (95% CI) 4.2 (2.3-7.9)

Cochrane analysis: Insufficient evidence of efficacy.

Beyond Meta-Analysis (IBS)

**Overall Effects**

**What About Pain?**

Things look better if you analyze per protocol. So, we can still claim a rationale.
Back to the Patient

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

α2δ as the Answer?

Gabapentin greatly reduced pain threshold in response to rectal distension.

Gut 2007;56:1218-1225

However...

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

Gut 2007;61:1228-1225
Back to the Patient

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

Opioids & Visceral Pain

- Anecdotal evidence
  - ER practice
  - Colonoscopy

![Graph showing prevalence of Opioids & Visceral Pain](image)

*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 for 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)

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?

Additional ‘post hoc’ info worked best in IBS-D; decreased bowel frequency.
No Acute Analgesic Effect in IBS

Clinical Gastroenterology and Hepatology 2007;5:1268-1275

Asimadoline in Functional Dyspepsia

Hypnotherapy

Cognitive behavioral therapy

Psychotherapy
Psychological Therapy
Global Improvement vs. Control

What About Pain?

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).