Chronic Abdominal Pain

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Pain is a BIG Problem

• Physicians have been encouraged to treat pain more aggressively over the last 20 years
• Controlled substance prescriptions have skyrocketed
• More episodes of oversedation, more abuse, more diversion of opiates
• New classes of non-narcotic pain medications are available and might be used in GI patients
Pain is a symptom that...

- May reflect tissue damage or injury
  - Nociceptive pain
- May occur in the absence of tissue damage or injury
  - Neuropathic pain
  - Psychogenic pain
- May be acute or chronic
- Has an extensive and complex differential diagnosis

Abdominal pain may arise from...

- Any intra-abdominal organ or structure
- Abdominal wall
- Extra-abdominal organs (referred pain)
Determining the cause of abdominal pain . . .

- Need to consider many possibilities
- History is key
  - Time course – acute vs. chronic, variation over time
  - Location of pain
  - Quality of pain
  - Initiating factors
  - Relieving factors
  - Relationships with eating, BMs, position, movement

Determining the cause of abdominal pain . . .

- Physical findings
  - Tenderness
    - Diffuse vs. focal
    - Relation to contraction of abdominal wall
  - Distention
  - Bowel sounds
  - Organomegaly
  - Associated symptoms
Structural visceral causes of abdominal pain

Inflammatory conditions of the upper abdomen:
Ulcer disease (duodenal ulcer, gastric ulcer)
Esophagitis
Gastritis
Pancreatitis
Cholecystitis
Choledocholithiasis
Hepatitis
Colitis

Cancers of the upper abdomen:
Hepatoma
Cholangiocarcinoma
Pancreatic cancer
Gastric cancer
Lymphoma

Inflammatory conditions in the mid-and lower abdomen:
Enteritis
Colitis
Diverticulitis
Structural visceral causes of abdominal pain

- **Bowel obstruction:**
  - Adhesions
  - Tumor
  - Inflammation
  - Intussusception, volvulus
  - Colon cancer

- **Vascular problems:**
  - Mesenteric vascular insufficiency
  - Abdominal aortic aneurysm

Abdominal pain due to other organ systems

- **Referred pain from the chest:**
  - Pneumonia
  - Pleurisy
  - Costochondritis
  - Chest wall injury

- **Urinary tract problems:**
  - Kidney stones
  - Urinary tract infection
  - Tumors of kidney or bladder

- **Pelvic problems in women:**
  - Ovarian cysts or cancer
  - Salpingitis, pelvic inflammatory disease
  - Ectopic pregnancy
  - Fibroid tumor of uterus
  - Malignant tumors of uterus
  - Endometriosis
  - Adhesions (scars)
Functional abdominal pain

Irritable bowel syndrome
Functional dyspepsia
Sphincter of Oddi dysfunction
Functional abdominal pain (not otherwise specified)

SHOULD BE DIAGNOSED BY CRITERIA. IF NONCONFORMING, BE SKEPTICAL ABOUT DIAGNOSIS.
Less common causes of abdominal pain

**Abdominal wall pain:**
- Port site pain, other scars
- Nerve entrapment syndromes
- Abdominal wall hernias
- Fibromyalgia

**Radicular neural pain:**
- Shingles, post-herpetic neuropathy
- Thoracic spine disorders
- Neuropathy
Less common causes of abdominal pain

Rare syndromes:

- Angioedema
- Porphyria
- Lead poisoning

Abdominal wall pain

- Most common overlooked cause of chronic abdominal pain
- Characteristically localized tenderness
- No relation to meals or bowel movements
- May be related to position or movement of abdominal wall
- Increased pain with tensing of abdominal wall (Carnett’s sign)
- Characteristic locations
Characteristic locations of abdominal wall pain

- Edge of rectus sheath
- Ileoinguinal nerve
- Ileohypogastric nerve
- Laparoscopy port sites

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18-item Anterior Cutaneous Nerve Entrapment (ACNES) Questionnaire

- Useful to distinguish ACNES from other causes of abdominal pain
- Cut-off score of 10 points
  - 94% sensitivity
  - 92% specificity

Treatment of abdominal wall pain

• Can confirm diagnosis by injection of trigger point with local anesthetic
• Repeat injection +/- corticosteroid may be useful
• Pain management: nerve block (neurolysis/neurotomy)
• Pain modification therapy
  • Tricyclic antidepressants
  • Gabapentin

Radicular nerve pain

• Somatic nerves (intercostal nerves) from thoracic spine mediate sensation on abdominal wall
• Can be affected by trauma, thoracic spine problems (disc disease, arthritis), postherpetic, or diabetic neuropathies
• Characteristically unilateral: pain does not cross midline
• Dermatomal distribution
• No relation to meals, bowel movements
• Constant pain, may be positional
• Intercostal nerve blocks diagnostic/therapeutic
Angioedema

- Hereditary angioedema may produce recurrent abdominal pain
- Diagnosis often delayed (on average by 8 years)
- Type I: reduced serum concentration of normal C1-esterase inhibitor (85% of cases)
- Type II: mutated/dysfunctional C1-esterase inhibitor
- Type III: normal levels and function of C1-esterase inhibitor; other problems present: coagulation factor XII, bradykinin

Porphyria

- Only acute porphyrias produce neurologic problems and abdominal pain
  - Acute intermittent porphyria
  - Hereditary coproporphyria
  - Variegate porphyria
  - ALA dehydratase deficiency
  - (NOT porphyria cutanea tarda, erythropoietic protoporphyria)
- Measure urine porphobilinogen during attacks
Drug Treatment of Abdominal Pain

Neurophysiology of pain

• Pain is a sensory experience created by the nervous system
  – Reflects inflammation, tissue injury
  – May result from dysfunction of pain recognition system
• Involves several layers of processing in periphery, spinal cord, brain
• Numerous potential targets for analgesics
Pain sensation involves several layers of processing...

- **Peripheral sensory nerves**
  - Nociceptors
    - Acute output proportional to stimulus
    - Sensitization may occur

- **Spinal cord**
  - Spinal interneurons – sensitization may occur
  - Descending pathways from brain – modulate pain

- **Brain processing** – emotional context added

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**Nociceptors**

- Primary afferent nerves
- “Free nerve endings” in tissues
- Transduce chemical, mechanical and thermal signals that accompany tissue injury
  - Receptors on dendrites (often ligand-gated ion channels) modify transmembrane potential
  - If sufficient stimulation, action potential travels centrally to dorsal horn of spinal cord
Types of receptors that function as nociceptors

- TRPA1  Transient receptor potential channel A1
- TRPM8  Transient receptor potential channel M8
- TRPV1-4 Transient receptor potential channel V1-4
- ASIC  Acid-sensing ion channel
- 5-HT  Serotonin receptor
- P2X  ATP-gated purine receptor
- TRKA  Tyrosine kinase receptor A
- GPCRs  G protein-coupled receptors

Primary Afferent Neurons

- If receptors produce enough depolarization of dendrite, action potential is triggered.
- Propagation of action potential depends on voltage-gated sodium channels opening sequentially
  – This process is blocked by local anesthetics
- Cell bodies of primary afferent neurons located in dorsal root ganglia near spinal cord
Primary Afferent Neurons

- Nerve terminals have voltage-gated calcium channels
- Depolarization of nerve terminal leads to calcium entry and neurotransmitter release onto dorsal horn neurons of spinal cord

Dorsal Horn Neurons

- Inputs from:
  - Primary afferent neurons
  - Interneurons
  - Descending inhibitory pathways
- Output to:
  - Spinothalamic tract
    - Intensity and localization of pain
  - Spinohypothalamic tract
    - Mediates autonomic responses to pain
Neuromediators in Dorsal Horn

- **Excitatory**
  - Glutamate
  - Substance P
  - Calcitonin gene-related peptide
  - Brain-derived neurotrophic factor
  - Bradykinin

- **Inhibitory**
  - Endogenous opioids
    - Encephalin
    - β-endorphin
  - γ-aminobutyric acid (GABA)
  - Glycine
  - 5-HT

**Receptors for these neuromediators trigger or inhibit output via spinothalamic tract**
Brain Processing

- Thalamus receives signal from spinothalamic tract
- Thalamic pathways distributed widely
  - Primary sensory cortex (WHERE is pain)
  - Limbic system, frontal lobes (AFFECTIVE response)
  - Hippocampus (MEMORY of pain)

Descending Inhibition

- Pathway from brain to various levels of spinal cord
- Release opioids, noradrenaline, 5-HT onto dorsal horn neurons
- Inhibit output of dorsal horn neurons and thereby reduce pain signaling to brain
Chronic Pain

- Sensitization
  - Peripheral
    - At level of nociceptors
  - Central
    - Dorsal horn neurons
    - Brain circuits

Pharmacology of Analgesia

- Opiates work primarily at spinal level to inhibit dorsal horn neurons
  - Effectively treat most forms of pain
  - Standard for potent analgesia
- Non-narcotic pain medications
  - Can approach effectiveness of opiates
  - Work at peripheral and central levels
  - May reduce sensitization

THESE DRUGS ARE NOT FDA-APPROVED FOR TREATING ABDOMINAL PAIN
Nonsteroidal Anti-inflammatory Drugs

• Prostaglandins sensitize nociceptors to other mediators
• NSAIDs reduce prostaglandin synthesis, reduce sensitivity of primary afferent neurons
• Useful in patients with abdominal wall pain, cancer
• Ketorolac (injectable NSAID) has efficacy close to morphine

• Side effects
  – Dyspepsia, ulcer disease
  – Gastrointestinal bleeding
  – Diarrhea
  – Renal dysfunction
  – Abnormal liver tests, jaundice
  – Impaired cartilage repair
• Drug interactions
Anticonvulsant Drugs

• Initially developed to reduce repetitive nerve discharges in brain associated with seizures
• Useful in neuropathic pain, later tried in other painful conditions:
  
  Central Pain  |  Post-sympathectomy pain  
  Porphyria    |  Fabry disease  
  Migraine     |  Multiple sclerosis  
  Phantom limb |  Diabetic & peripheral neuropathy  

Anticonvulsant Drugs

• Carbamazepine*  
• Oxcarbazepine  
• Topiramate*  
• Levetiracetam  
• Pregabalin*  
• Gabapentin*  
• Zonisamide  
• Lamotrigine

*FDA-approved for some painful condition (e.g., neuralgia, migraine, fibromyalgia)
Carbamazepine

- Structurally related to tricyclic antidepressants
- Inhibits norepinephrine uptake, blocks sodium channels
- Typical doses: 800—1200 mg daily
- Taken with food to avoid gastric distress
- Adverse effects: sedation, nausea, diplopia, vertigo, aplastic anemia, agranulocytosis, pancytopenia, thrombocytopenia, ↑ liver tests
- Check CBC, liver tests regularly

Gabapentin

- Resembles structure of GABA (but does not interact with GABA receptor)
- Precise mechanism of action uncertain
- Titrate dose up to a maximum of 1200 mg TID
- Reduce dose for renal insufficiency
- Adverse effects: somnolence, dizziness, ataxia, fatigue, inability to concentrate, gastrointestinal disturbances, nystagmus, pedal edema
Pregabalin

- GABA analog, interacts with GABA receptor
- Binds to voltage-gated calcium channel
- Effective doses: 50—200 mg TID
- Adverse effects: dizziness, somnolence, headache
- Regulated as a controlled substance due to potential for CNS depression (Schedule V)

Neuromuscular Drugs

- Baclofen: GABA-B receptor agonist
  - Used in “pain pump” cocktail
  - Adverse effects common
- Cyclobenzaprine: related to tricyclics
- Methocarbamol, metaxalone: skeletal muscle relaxants
  - Adjunctive to other analgesics
**α-Adrenergic Agonists**

- **Clonidine**
  - Can mitigate opiate withdrawal syndrome
  - For “analgesic” effects, patch delivery system best
  - Antihypertensive effect may be limiting
  - Adverse effects: dry mouth, drowsiness, fatigue, headache, lethargy, sedation, dizziness

- **Tizanidine**
  - Another α-adrenergic agonist

**Antidepressant Drugs**

- **Tricyclic antidepressants**
  - Inhibit serotonin and norepinephrine reuptake
  - Increase effectiveness of descending inhibitory pathway
  - Best thought of as “pain modifiers”
  - Effective in low doses (10—25 mg nightly)
  - May take weeks to have beneficial effect
  - Side effects: anticholinergic (constipation, dry mouth, tachycardia), weight gain, sedation
  - Use with caution in elderly (falls); contraindicated with narrow angle glaucoma, heart block, recent MI
Antidepressant Drugs

- Selective serotonin reuptake inhibitors (SSRI)
  - Less evidence of effectiveness for pain than TCAs
  - Antidepressant effects substantial
  - Adverse effects: headache, stimulation or sedation, fine tremor, akathesia, nausea, vomiting, anorexia, bloating, diarrhea, decreased sexual function

- Serotonin—norepinephrine reuptake inhibitors (SNRI)
  - Duloxetine approved for diabetic neuropathy, fibromyalgia, chronic musculoskeletal pain
  - Adverse effects similar to SSRIs, ? less sexual problems

Use of Non-narcotic Pain Medications in Gastroenterology

- Limited evidence in a limited number of conditions
- Generalizability of evidence is uncertain
- Use with caution
- Pay attention to side-effects
- Seek pain management consultation if you are insecure about using these agents
Non-cardiac Chest Pain

• Recent meta-analysis (Nguyen & Eslick, 2012*)
  – 6 RCTs identified (placebo vs. paroxetine, sertraline, imipramine, venlafaxine, trazodone)
  – All except imipramine improved clinical global rating score
  – Significant percentage of pain reduction (vs. placebo)
    • Venlafaxine 50% (vs. 10%)
    • Sertraline 63% (vs. 15%)
    • Imipramine 52% (vs. 1%)
  – Improvement in pain control correlated with reduced depression scores

  *Aliment Pharmacol Ther 2012;35:493-500

Irritable Bowel Syndrome

• Evidence of benefit from antidepressants has been mixed
• Cochrane review showed that 54% of IBS patients treated with antidepressants had less pain (vs. 37% with placebo, RR 1.49, 95%CI 1.05—2.12, P = 0.03, NNT = 5)*
• SSRIs tended to improve global assessment, TCAs helped abdominal pain and symptom scores

Summary

• Abdominal pain is a common problem that often is due to visceral causes
• When no anatomic problem is documented, functional syndromes may be diagnosed; be sure that criteria are met
• Abdominal wall pain is the most commonly overlooked cause of chronic abdominal pain
• Other frequently misdiagnosed problems include radicular nerve pain, angioedema, acute porphyrias

Summary

• There are good reasons to theorize that non-narcotic pain medicines could work in many painful gastrointestinal conditions
• Evidence is lacking for benefit from most of these drugs for most gastrointestinal conditions
• Off-label use may be reasonable if the alternative is long-term opiate therapy