Understanding and Managing the Patient with Chronic and Severe Abdominal Pain

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Leading Gastrointestinal Symptoms Prompting an Ambulatory Visit

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Estimated no. of visits (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain</td>
<td>12</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
</tr>
<tr>
<td>Anorectal symptoms</td>
<td>1</td>
</tr>
</tbody>
</table>

Case History (HPI)

- 33 yo F referred with chronic and severe abdominal pain, nausea, and constipation refractory to prior treatments.
- Recurrent abdominal pain age 6 → school absences; pain increased after menarche with dysmenorrhea.
- Age 19 after traveling through Mexico → acute GE with pain, fever, diarrhea, vomiting → Dx. IBS-D.
- Over last 10 years pain more frequent; changes to IBS-C.
- Over last 5 years, pain is constant associated with bloating and constipation with straining; not relieved with bowel movement.
- Also has fibromyalgia and migraines.
Case History (PMH)

• Meds: Antispasmodics, PPI, gabapentin, have not helped the pain, PEG solution has not helped the constipation

• Procedures: 2 colonoscopies, EGD, CT scan, capsule endoscopy, pelvic US, abdominal MRI neg.

• Exploratory lap 5 years ago → ? endometriosis → no response to leuprolide acetate

• Cholecystectomy 3 years ago due to low ejection fraction on HIDA

Case History (PMH con’t.)

• Over 30 ER visits → receives morphine + ondansetron; D/C with week’s supply of hydrocodone or oxycodone

• FP refills narcotics to prevent repeat ER visits

• 5 hospitalizations for pain when ER Rx unsuccessful

• Hospitalization (1 month ago)
  - 2nd exploratory laparotomy negative
  - Post op → increasing IV morphine (60 mg/day) needed for pain
  - Unable to discharge because of continued pain
Case History (PMH con’t.)

• Psychiatry consultation
  • Major depression and PTSD from childhood deprivation and sexual/physical abuse
  • Parents divorced when patient was 12
  • Left home at age 16, pregnant at age 17
  • Left spouse after 4 years because of physical abuse
  • Currently living with mother
  • Last 2 years unable to work, on disability
  • Recommends paroxetine 20 mg. and f/u at local MHC

• Discharged on paroxetine and oxycodone 10 mg. tid

Case History (current visit)

• Curled on side on table with hips flexed

• Severe cramping pain in mid and lower abdomen with nausea

• Constipation has gotten worse

• Abdominal exam – generalized tenderness and fullness on right and left overlying colon

• Requests hospitalizations to get IV pain medication
Case History - Discussion

- What are your general observations, thoughts and feelings?
Symptom-Related Behaviors

Mrs. Jones is here. HELP ME! what do I do?

Expressing pain of varying intensity through verbal and nonverbal methods

Seeking health care frequently

Taking limited personal responsibility for self-management

Urgent reporting of intense symptoms

Focusing attention on complete relief of symptoms

Minimizing a potential role for psychosocial contributors

Requesting diagnostic studies

Making requests for narcotic analgesics
Case History - Discussion

• What are your general observations, thoughts and feelings?

• What are the main GI diagnoses?
  • RAP (age 6)
  • PI-IBS with diarrhea (age 19)
  • IBS-C (age 23-28 – currently)
  • CAPS (age 28 – currently)
  • OIC (age 28 – currently)
  • NBS (age 28 – currently)
Rome Working Team Report  
Post-Infection Irritable Bowel Syndrome

1. Recurrent abdominal pain at least 1 day/week in the last 3 months with symptom onset at least 6 months before diagnosis
   Associated with ≥ 2 of the following
   
   - Related to defecation
   - a change in frequency of stool
   - a change in form (appearance) of stool

2. Symptom development immediately after acute infectious GE

3. Infectious GE defined by positive stool culture or ≥ 2 of:
   - Fever
   - Vomiting
   - Diarrhea

4. Should not meet criteria for IBS before onset of acute illness

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Conceptual Model – Postinfection IBS

- Infection
- Microbial virulence
- Gastroenteritis
- Impaired bacterial recognition
- Intestinal permeability
- Inefficient down regulation of the inflammatory response
- Low grade inflammation
- Genetic susceptibility
- Microbiota
- Stress
- Abuse/War trauma
- PI-IBS

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Barbara G, Grover M. Gastroenterology 2019; 156:46-58

Collins SM, Am J Gastro suppl 2012:1:2
Interrelated Enteric Factors Associated with Visceral Sensitization and FGIDs

- Inflammation/immune reactivity
  - Cytokines
  - Lymphocytes
  - Mast cells
- Gut flora
  - Altered microbiome
- Increased Intestinal Permeability

Mast Cells Infiltrate and Associate With Nerve Fibers in Colonic Mucosa of IBS Patients

Activated mast cell (MC) with degranulation polarized toward adjacent nerve (N)

Stress Activates Neuronal CRH Release with Mast Cell Degranulation

- CRH
- ACh
- Nerve fibers
- Intestinal mucosa
- Mucus layer
- Epithelial cells
- Mast cell
- Granulocyte
- B cell
- T cell

Stress

Intestinal mucosa

Mucosal barrier

Nerve sensitized

T-Cell

Intestinal mucosa

Stress Activates Neuronal CRH Release with Mast Cell Degranulation

- Bacterial products
- Mast cell degranulation
- TNFα
- Tryptase
- PGE2
- Histamine
- ACh
- CRH
- Nerve sensitized

Intestinal barrier permeable

Mucus layer

Visceral Sensitization: Hyperalgesia and Allodynia

- Pain sensation
- Stimulus intensity
- Normal
- Innocuous
- Noxious
- Hyperalgesia
- Allodynia

Stimulus intensity

Insult
FC: Functional constipation
FDr: Functional diarrhea
IBS-C: Irritable bowel syndrome with predominant constipation
IBS-D: Irritable bowel syndrome with predominant diarrhea
IBS-M: Irritable bowel syndrome with mixed bowel habits (D and C)
What Are the Effects of Opioids on the Gastrointestinal Tract

- Decrease transmitter release from enteric interneurons and motor neurons
- Suppress propagating propulsive contractions
- Alter the firing properties of intrinsic sensory afferent neurons
- Reduce excitability of secretomotor neurons
- Increase sympathetic outflow to GI tract
- Peripheral and central sensitization (with chronic use)

% with >10 antispasmodic prescriptions increased annually (p<.001)
% with gut-brain neuromodulator prescriptions did not change annually (p=.07)*
% with > opioid prescriptions decreased annually (p<.001)

* gut brain neuromodulator includes antidepressants (TCA, SSRI, SNRI, mirtazapine) and pregabalin/gabapentin

Chen FW, et al. Gastroenterology in press, 2019
### Relationship of Chronic Opioid Use, OBD, OIC, and NBS

**Chronic opioid users**

- **OBD** 50-60%
- **OIC** ~40%
- **NBS** ~5%

Kurlander, JE and Drossman, DA, Nat Rev Gastroenterol Hepatol 2015; 11:410

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### Adverse Effects of Opioids on the Bowel

- **Opioid Bowel Dysfunction (OBD)**
  - Effects of opioids on GI system: constipation, nausea, vomiting, bloating, ileus, and pain

- **Opioid Induced Constipation (OIC)**
  - Development of constipation symptoms (harder or infrequent stools, straining, incomplete evacuation) when put on opioids

- **Narcotic Bowel Syndrome**
  - Abdominal pain is the predominant symptom
  - Progressive and paradoxical increase in pain despite continued or escalating dosages of narcotics prescribed to relieve the pain
  - Improves with detoxification

Grunkenmeler et al, Clin Gastro Hep 2007;5:1126
### Current Treatments for Opioid-Induced Constipation

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Mode / Action</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relistor</td>
<td>Salix / Valient</td>
<td>μ-opioid receptor antagonist</td>
<td>SQ, Oral</td>
</tr>
<tr>
<td>Methylaltrexone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Movantik</td>
<td>A-Z</td>
<td>Pegylated μ-opioid receptor</td>
<td>Oral</td>
</tr>
<tr>
<td>Naloxegol</td>
<td></td>
<td>antagonist</td>
<td></td>
</tr>
<tr>
<td>Amitiza</td>
<td>Takeda, Sucampo</td>
<td>CIC-2 chloride channel</td>
<td>Oral</td>
</tr>
<tr>
<td>Lubiprostone</td>
<td></td>
<td>activator</td>
<td></td>
</tr>
<tr>
<td>Linzess / Constella</td>
<td>Ironwood Almiral</td>
<td>Guanylate cyclase 2C agonist</td>
<td>Oral</td>
</tr>
<tr>
<td>Linclotide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolor / Resotran</td>
<td>Shire</td>
<td>5-HT4 receptor agonist</td>
<td>Oral</td>
</tr>
<tr>
<td>Prucalopride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entereg</td>
<td>GSK</td>
<td>μ-opioid receptor antagonist</td>
<td>Oral (ileus only)</td>
</tr>
<tr>
<td>Alvimopan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targin / Targinact</td>
<td>Purdue, Mundipharma</td>
<td>opioid + μ-opioid receptor</td>
<td>Oral</td>
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<tr>
<td>Oxycodeine / naloxone</td>
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<td>antagonist</td>
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<tr>
<td>Naldemedine</td>
<td>Shionogi &amp; Co, Ltd</td>
<td>m, k, and d opioid receptor</td>
<td>Oral</td>
</tr>
<tr>
<td>S-297995</td>
<td></td>
<td>antagonist</td>
<td></td>
</tr>
</tbody>
</table>

“I'm afraid that your irritable bowel syndrome has progressed. You now have furious and vindictive bowel syndrome.”
Repetitive Mechanical Stimulation Sensitizes the Spinal Cord

CNS Contribution to GI Pain
- Centrally mediated abdominal pain (CAPS)
- Functional GI disorders
  - IBS
  - Functional dyspepsia
- Chronic GI disorders
  - GERD
  - IBD
- Acute GI episodes
  - Bowel obstruction
  - Cholecystitis
### Spectrum of Severity: IBS and CAPS

<table>
<thead>
<tr>
<th></th>
<th>Mild IBS</th>
<th>Moderate IBS</th>
<th>Severe IBS</th>
<th>CAPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Est. Population Frequency (%)</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Abdominal Pain Severity</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Episode Frequency</td>
<td>occasional</td>
<td>frequent</td>
<td>frequent to constant</td>
<td>constant</td>
</tr>
<tr>
<td>Psychosocial Diagnosis</td>
<td>0 to +</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Health Care Utilization</td>
<td>0 to +</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>0</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Gut-Brain Influence</td>
<td>Gut&gt;&gt;CNS</td>
<td>Gut&gt;CNS</td>
<td>CNS&gt;Gut</td>
<td>CNS</td>
</tr>
</tbody>
</table>

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### Rome IV Diagnostic Criteria* for Centrally Mediated Abdominal Pain Syndrome**

Must include all of the following

- Continuous, or nearly continuous, abdominal pain
- No or only occasional relationship of pain with physiological events (eg, eating, defecation, or menses)†
- Pain limits some aspect of daily functioning††
- The pain is not feigned
- Pain is not explained by another GI disorder or medical condition

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* Criteria fulfilled for the last 3 months, with symptom onset at least 6 months prior to diagnosis

** CAPS is typically associated with psychosocial comorbidities, but there is no specific psychosocial profile that can be used for diagnosis of CAPS

† Some degree of GI dysfunction may be present

†† Limitation of daily functioning includes impairments in work, intimacy, social/leisure, family life, and caregiving for self or others
Visceral Hypersensitivity in IBS, But Not FAPS


Percentage of patients with condition

Peripheral factors
- Food
- Acute GI infection
- Mucosal inflammation
- Abdominal/pelvic surgery
- Menses

Psychosocial variables
- Life stress
- Somatization
- Anxiety disorder
- Depression
- Poor coping skills
- Poor social support
- Maladaptive cognitions
- Abuse

CAPS
Disinhibition

IBS
Afferent Excitation

Narcotic Bowel Syndrome
(Opioid induced central hyperalgesia)

The Narcotic Bowel Syndrome: Clinical Features, Pathophysiology, and Management

David M. S. Grunkemeier, Joseph E. Cassara, Christine B. Dalton, and Douglas A. Drossman

Rome IV Diagnostic Criteria* for Narcotic Bowel Syndrome (NBS)/Opioid-Induced Hyperalgesia

Must include all of the following

1. Chronic or frequently recurring abdominal pain** that is treated with acute high-dose or chronic narcotics

2. The nature and intensity of the pain is not explained by a current or previous GI diagnosis†

3. Two or more of the following:
   • The pain worsens or incompletely resolves with continued or escalating dosages of narcotics
   • The pain markedly intensifies when the narcotic dose is reduced and subsides when narcotics are re-instituted ("soar and crash")
   • There is a progression of the frequency, duration and intensity of pain episodes

* Criteria fulfilled for the last 3 months, with symptom onset at least 6 months prior to diagnosis
** Pain must occur most days
† A patient may have a structural diagnosis (e.g., IBD, chronic pancreatitis), but the character or activity of the disease process is not sufficient to explain the pain

Keefer L, Drossman DA, Gastroenterology 2016; 150:1408
Case History - Discussion

- What are your general observations, thoughts and feelings?
- What are the main GI diagnoses?
- What are the psychosocial/behavioral features?
  - Illness anxiety and somatic symptom disorder (DSM5)
  - Major depression
  - PTSD (physical and sexual abuse)
  - Reluctance to come off opioids
Outcome Study - Sexual Abuse and Health Status

- Pain (VAS 0-100)
- # Non-GI Sx
- # Days disabled
- # Surgeries
- Psych. distress (SCL-90) x 10
- Funct. Disability (SIP)

* = p<0.05
** = p<0.01

Abuse Severity* and Number of Health Care Visits During One Year (n=196)

p=0.0003

*Abuse Severity Scale (0=no abuse, 6=severe)
Case History - Discussion

• What are your general observations, thoughts and feelings?

• What are the main GI diagnoses?

• What are the psychosocial/behavioral features?

• What are the key pathophysiological features for severe refractory GI pain?

Pain Is a Modifiable Experience

Psychosocial context
- Pain beliefs
- Cultural schema
- Expectation
- Conditioning

Cognitions
- Hypervigilance
- Attention
- Distraction
- Catastrophizing

Chemical/Structural
- Neurodegeneration
- Metabolic (opioidergic, dopaminergic)
- Maladaptive plasticity

Mood
- Depression
- Anxiety

Genetics

Peripheral and central sensitization

Nociceptive modulation

Amplified input
Nutrients

Physiological stimuli

Salient/noxious stimuli

Neurohormonal signals

Gastrointestinal distension, contraction and relaxation

Homeostatic system

Sensory filtering

Overlapping Networks in Altered Visceral Sensation

Prefrontal cortical modulatory regions

LPFC, MPFC and BA40

Modulation of response to interoceptive input

Overactive reward system

Impaired descending modulatory system

Overactive affective circuit

Impaired cognitive circuit

Homeostatic system

Reward system

Cognitive circuit

Descending modulatory system

Impaired sensory filtering

Sensory filtering

Impaired homeostatic system

Cognitive circuit

Affective circuit

Emotional-arousal network

Emotional response to sensation

Homeostatic-afferent network

Input from the GI tract

Moderation of response to interoceptive input

Overactive homeostatic system

Impaired affective circuit

Impaired descending modulatory system

Van Oudenhove L and Aziz Q Nat Rev Gastroenterol Hepatol 2013

Neuroplasticity, Neurogenesis and Augmentation

- Abuse, FGIDs and other chronic pain conditions are associated with reduced neuronal density in brain pain control areas

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Ringel Y, Drossman DA, Gastroenterology 2008; 134:396

Drossman DA Am J Gastroenterology 2009; 104:2897
Hippocampal Volume and Delayed Memory Loss In Gulf War Related PTSD

Hippocampus head volume

Wechsler delayed verbal memory

Correlation delayed memory with hippocampal volume \( V=0.38 \) (\( p<0.001 \))


CNS Neuroplasticity: Reduced Brain Volume/Gray Matter

Major Depression and Bipolar Disorder
- ACC and orbitofrontal cortex
  (Konarski JZ et al. Bipolar Disorders 2008; 10:1-37)

Sexual/Physical abuse
- Hippocampus
  (Bremner D et al Biol Psychiatry; 1997;41:23-32)

Chronic Somatic Pain
- ACC, PCC, VMPFC
  (Valet M et al. Psychos Med 2009;71;49)

Irritable Bowel Syndrome
- dACC (aMCC)
  (Blankstein U et al. Gastroenterology 2010;138:1783)

Painful Chronic Pancreatitis
  (Frøkjær, Clin Gastroenterol Hep 2012; 10:436)
Altered Brain Structure in IBS

Cortical thinning in anterior MMC

![Brain Image]

**Case History - Discussion**

- What are your general observations, thoughts and feelings?
- What are the main GI diagnoses?
- What are the psychosocial/behavioral features?
- What are the key pathophysiological features for severe refractory GI pain?
- What would be the management approach?
Graded Treatment Response

- Multidisciplinary approach
- Psychological treatments
- Central Neuromodulators
  - Improve functioning
- Manage stress
- Gut Pharmacotherapy
  - Improve functioning
- Diet, lifestyle advice
- Positive diagnosis
- Explain, reassure

Brain-Gut Influences on Severity and Treatment

- Injury
- Infection
- Diet
- Hormones, Peptides
- Life stress
- Psych Dx
- Poor coping
- Abuse

Afferent excitation

- Lifestyle
- Gut medications
- Antidepressants
  - Augmentation Rx
- Diet
- Probiotics
- Behavioral Rx

Disinhibition

Mild
Moderate
Severe
Narcotic Bowel Syndrome

Diagnosis, Characterization, and 3-Month Outcome After Detoxification of 39 Patients With Narcotic Bowel Syndrome


Abdominal Pain Scores

Pre-detoxification n=39
Post-detoxification n=37
Stayed off narcotics n=13
Went back on narcotics n=10
3 month follow-up
Two weeks post opioid detoxification

29 yo with NBS taking 80 mg. dilaudid (400 mg morphine equivalent) /day and pain level as 10/10. She was unable to eat or handle feeding tube because of pain and she had been on TPN for 6 months. Inpatient detoxification occurred per protocol over 6 days. She began eating 2 days after discharge.

Drossman DA (chair), Tack J (co-chair), Ford AC, Szigethy E, Tornblom H, Van Oudenhove L. Gastroenterology 2018;154:1140-1171

Redefine Psychotropics: Gut-Brain Neuromodulators

“Consistent with the Rome Foundation’s new definitional guidelines, we relabel agents working both in the brain and gut as “gut-brain neuromodulators”:

● Central Neuromodulators (e.g. antidepressants, anti-anxiety or antipsychotics) and

● Peripheral Neuromodulators (e.g., serotonergic, chloride channel, delta ligand agents, etc.).

“We believe this new terminology will improve understanding of their pharmacological value, reduce stigma, and likely improve treatment adherence.”
Neuromodulators

- **Central Neuromodulators**
  - **Antidepressants**
    - TCA (desipramine, nortriptyline, amitriptyline, imipramine)
    - SNRI (duloxetine, milnacipran, venlafaxine, desvenlafaxine)
    - Tetracyclics (mirtazapine, trazadone, mianserine)
    - SSRI (citalopram, escitalapram, fluoxetine, paroxetine)
  - **Atypical Antipsychotics** (quetiapine, olanzapine, aripiprazole, levosulpiride)
  - **Azapirones** (buspirone, tandospirone)
  - **Anticonvulsants** (levetiracetam, zonisamide, topiramate)
  - **NMDA Receptor Antagonists** (memantine, dextromethorphan, ketamine)

- **Peripheral Neuromodulators**
  - **α2ƍ ligands** (gabapentin, pregabalin)
  - **Serotonergic (5HT) agents** (alosetron, prucalopride)
  - **Chloride channel agents** (e.g. linaclotide, plecanatide)

- **Opioids**
  - **Narcotics** (oxycodone, hydrocodone, hydromorphone, codeine)
  - **μ agonist, γ antagonist** (eluxadoline)
  - **Loperamide**

Rationale for Central Neuromodulators

- **Treatment of psychiatric and brain gut disorders associated with pain**

- **Peripheral effects**
  - Motility / secretion
  - Reduces nerve signals from gut (TCA)

- **Improves the brain’s pain regulation**

- **May enhance nerve cell regrowth (neurogenesis)**
**Ascending Visceral Pain Pathway**

- **pACC**
- **MCC**
- **Insula**
- **Thalamus**
- **Reticularthalamic**
- **Spinothalamic**
- **Spinoreticular**
- **Spinomesencephalic**
- **Dorsal reticular nucleus**
- **Spinal afferent**

**Descending Visceral Pain Pathway**

- **pACC**
- **mPFC**
- **Thalamus**
- **PAG**
- **Locus coeruleus**
- **Caudal raphe nucleus**
- **Noradrenergic**
- **Serotonergic**
- **Rostral ventral medulla**
- **Spinal afferent**
- **Opioid**
Effect of Depressed Mood on Central Pain Registration from Noxious Heat Stimulus in Healthy Subjects

Berna C et al. Biol Psychiatry 2010; 67:1083

Pain

Mood:

Neutral

Depressed

Z scores 2.3 4 2.3 4 -2.3 -4

IBS - Antidepressants

TCA (NE effect) SSRI (5HT effect)

Orocecal transit time (min)

Controls IBS Controls IBS

Baseline Imipramine P<0.05

Baseline Imipramine P<0.05

Baseline Paroxetine P<0.05

Baseline Paroxetine P<0.05

Gorard, Am Pharmicol 1994; 35:203
Response to Noxious Colorectal Distension in Rats

Afferent nerve discharge (% control)

Su, Pain, 1998; 76:105

TCA's and SNRI's Reset Dysfunctional Pain Regulation at the Brainstem via Descending 5-HT and NA Activation

Important target for drug development
Neurogenic Theory of Depression and Antidepressant Treatment

Genes and early life stress

Social stress, drug abuse, medical illness

Trigger

Critical threshold leading to depression

Uncoupling of affect from context

Dentate neuron vulnerability

Dentate neurons

Basal neurogenesis

Stress

Suppressed neurogenesis

Treatment

Restored neurogenesis


Changes in Gray Matter of Patients in Pain Before and Without Pain After Hip Surgery

Before surgery
n=32

Decrease in gray matter with pain (relative to controls)

After surgery
n=10 at 4 months

Increase in gray matter with no pain (relative to pre-surgery)

Effect of Imipramine vs. Placebo on Cognitive Function in Traumatic Brain Injured (TBI) Mice

% of time in NOR†

Weeks after injury

1 2 3 4
Weeks

† Novel Object Recognition Task

Effect of Imipramine vs. Placebo on Hippocampal Cell Proliferation in Traumatic Brain Injured (TBI) Mice

Ki67-positive cells (100x)
Rome IV: Chronic or Recurrent Painful FGIDs

- **Esophageal**
  - Functional Chest Pain
  - Functional Heartburn
- **Gastroduodenal**
  - Functional Dyspepsia - EPS
  - CVS
- **Bowel**
  - IBS
- **GB and Sphincter of Oddi**
  - Biliary pain
- **Centrally Mediated Disorders of GI Pain**
  - CAPS
  - NBS
- **Anorectal Disorders**
  - Functional Anorectal Pain (e.g., levator ani syndrome)
Pharmacological Properties of the Four Major Classes of Central Neuromodulators

A
[Tricyclic] Antidepressants

B
Selective serotonin reuptake inhibitors

C
Serotonin noradrenaline reuptake inhibitors

D
Noradrenergic and specific serotonergic antidepressant

Antidepressant Receptor Site Effects

<table>
<thead>
<tr>
<th>TCA (25-150 mg)</th>
<th>NE</th>
<th>5HT</th>
<th>Histamine</th>
<th>Ach</th>
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<tbody>
<tr>
<td>Amitriptyline (3o)</td>
<td>+++</td>
<td>+++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Doxepin (3o)</td>
<td>++</td>
<td>+++</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Desipramine (2o)</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nortriptyline (2o)</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

SSRIs (1-2 pills)

| Citalopram               | nil  | ++++ | nil       | nil   |
| Escitalopram             | nil  | ++++ | nil       | nil   |
| Fluoxetine               | nil  | ++++ | nil       | nil   |
| Paroxetine               | nil  | ++++ | nil       | nil   |
| Sertraline               | nil  | ++++ | nil       | nil   |

SNRI's (variable)

| Venlafaxine              | ++   | ++   | nil       | nil   |
| Duloxetine               | +++  | +++  | nil       | nil   |
| Milnacipran              | +++  | ++   | nil       | nil   |
Chronic or Recurrent Painful FGIDs

- **TCAs**
  - Low to modest doses (25-75 mg/day) have the most convincing evidence of benefit – re-evaluate dosing 4-6 weeks
  - Can adjust dosing up to 150 mg.
  - 2° amines (desipramine, nortriptyline) have fewer anticholinergic side effects than 2° amines (amitriptyline, imipramine)
  - Reduces diarrhea for IBS-D; may worsen constipation for IBS-C

- **SNRIs**
  - SNRIs (full dosing) have at least equal benefit for chronic GI pain based on data treating other chronic painful (somatic) disorders
  - Fewer side effects (nausea, mild constipation)
  - Higher doses needed using venlafaxine over duloxetine

- **SSRIs**
  - Is not helpful for chronic pain *per se*
  - Consider if anxiety is the dominant feature over pain
  - May help for constipation if present

---

**Psychological Therapies**

Subgroup analysis according to type of therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Trials</th>
<th>N</th>
<th>RR 95% CI</th>
<th>NNT 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive behavior therapy</td>
<td>7</td>
<td>491</td>
<td>0.60</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.42 – 0.87</td>
<td>2-7</td>
</tr>
<tr>
<td>Relaxation training</td>
<td>5</td>
<td>234</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.63-1.08</td>
<td></td>
</tr>
<tr>
<td>Dynamic psychotherapy</td>
<td>2</td>
<td>273</td>
<td>0.60</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.39-0.93</td>
<td>2-25</td>
</tr>
<tr>
<td>Hypnotherapy</td>
<td>2</td>
<td>40</td>
<td>0.48</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.26-0.87</td>
<td>1.5-7</td>
</tr>
</tbody>
</table>

*Ford AC et al. BMJ 2008; 337:a2313*
## Choosing the Right Candidates for GI Behavioral Therapy

<table>
<thead>
<tr>
<th>Likely to Benefit</th>
<th>Unlikely to Benefit/Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Has been told by provider that s/he has disorder of gut-brain interaction</td>
<td>• Severe depression or other psychopathology</td>
</tr>
<tr>
<td>• Is open to the possibility of behavioral change to alleviate symptoms</td>
<td>• Personality disorder</td>
</tr>
<tr>
<td>• Can make connections between stress, anxiety, thoughts and his/her symptoms</td>
<td>• Anorexia nervosa or severe ARFID</td>
</tr>
<tr>
<td>• Agrees that his/her coping could be improved</td>
<td>• No insight into the gut-brain interaction; fixated on a “cure”</td>
</tr>
<tr>
<td>• Has time to participate in therapy</td>
<td>• Unable to commit to treatment</td>
</tr>
<tr>
<td></td>
<td>• Substance abuse</td>
</tr>
</tbody>
</table>

## Augmentation Treatment

- Use more than one treatment to enhance benefit
- Can use lower dosages and minimize side effects
- Helpful when one treatment not successful or produces side effects
- Use with refractory GI painful disorders

**Examples**
- Add TCA or SNRI to peripheral GI agent for bowel symptoms
- Add Pregabalin/gabapentin to TCA or SNRI (e.g., for abdominal wall pain)
- Add Buspirone or Bupropion to antidepressant
- Combine SSRI and TCA
- Add atypical antipsychotic (e.g. quetiapine) to TCA or SNRI
- Combine antidepressant and psychological treatment

*Drossman DA, Am J Gastro 2009;104:2897*
Patient - Physician Relationship

Symptomatic medical treatment

Psychiatric referral

CBT

Hypnosis

IP psychotherapy

Stress management

Combined AD + psych

Augmentation

"2 drugs"  
/ 4-6 wks*  
Increase dose  
/ 4-6 wks*  
Low dose TCA or SNRI or SSRI

Symptomatic medical treatment

Patient - Physician Relationship

* Monitor side effects

Gut-brain modulators for Functional GI Disorders

SSRIs
(paroxetine, fluoxetine, sertraline, citalopram, escitalopram)

When anxiety, depression, and phobic features are prominent with FGIDs

TCAs
(amitriptyline, nortriptyline, imipramine, desipramine)

First-line treatment when pain is dominant in FGIDs

Tetracyclic antidepressant
(mirtazapine, mianserin, trazodone)

Treatment of early satiety, nausea/vomiting, weight loss and disturbed sleep

SNRIs
(duloxetine, venlafaxine, desvenlafaxin, milnacipran)

Treatment when pain is dominant in FGIDs or when side effects from TCAs preclude treatment

Augmentation

Azapirones (buspirone, tandospirone)
Dyspeptic features, anxiety prominent

Delta ligands (gabapentin, pregabalin)
Abdominal wall pain, comorbid fibromyalgia

SSRI
When anxiety and phobic features dominant

Atypical antipsychotics
Pain with disturbed sleep (quetiapine) anxiety, nausea (olanzapine, sulpiride) additional somatic symptoms ("side effects") other affective spectrum

Bupropion
Fatigue and sleepiness prominent

Psychological Treatment
CBT when maladaptive cognitions and catastrophizing present DBT, EMDR with history of PTSD or trauma

Hypnosis, Mindfulness, Relaxation as alternative treatments

Drossman DA et al. Gastroenterology 2018;154:1140-1171
Relapse Prevention

- Continued treatment with a central neuromodulator after clinical benefit achieved may reduce the likelihood of relapse or recurrence
- May relate to promoting neurogenesis
- Continue treatment 6-12 months after initial treatment response
- Evidence from a meta-analysis in psychiatry of 4000 patients with depression: continued treatment with an antidepressant reduced the odds of relapse by 70%*

* Geddes JR et al. 2003, Lancet; 361:653

Pharmacogenomic Testing

- Pharmacogenomics: The study of the variability of expression of genes relevant to disease susceptibility and drug response
  - Polymorphisms may predispose to FGIDs
  - Genetic variations may influence medication response via effects on drug metabolism (e.g., CYP2D6 isoenzyme affects plasma levels of TCAs)
- Pharmacogenomic testing (PGx)
  - Buccal brush assay (~$300) sent to lab
  - Reports summarize lifelong metabolism profiles of 100s of medications
  - Valuable for most all neuromodulators (limited for GI drugs)
  - Results indicate degree of high or low metabolizer status
  - Can be used to assess patient side effects or suboptimal treatment response or drug interactions
Key Points From the Interview

- Validated the symptoms and gave results of the evaluation
- Stated the diagnoses and using diagrams gave clear physiological explanations
- Described the vicious cycle of pain contributing to distress and distress lowering pain threshold (Brain-gut axis)
- Assessed the patient’s understanding
- Focused on management; additional studies not offered
- Gave rationale for neuromodulators using common examples
- Set up realistic expectations for a satisfactory outcome
- Worked together in decision making: accepted her choice not to come off opioids (yet)
- Agreed to continue work with patient and not abandon
Inhibitory Pathway

Pain Gate

Pain Regulation – Gate Control Theory

GI Drugs

Intestinal Afferent Receptor

Midbrain

Pain

Inhibitory Pathway

Two Last Items

- Have I answered all your questions?
- Regardless of how things go we will continue to work on this together
End