Psycho-pharmacologic Therapy for Functional Bowel Disorders

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Objectives

• Explore current theories on the pathophysiology of functional bowel disorders

• Analyze research which supports the use of psycho-pharmacologic and psychological therapies for symptom relief

• Identify particular psychotropic medications to utilize in common clinical situations
**Definition of FGID**

- Chronic and recurrent symptoms of the gastrointestinal (GI) tract:
  - without detectable structural or biochemical abnormalities
  - symptoms include: pain, nausea, vomiting, bloating, diarrhea and/or constipation
- Functional bowel disorders (FBDs) are a subgroup of functional gastrointestinal disorders

**Common Features of FBD**

- Pathophysiology
- Role of psychosocial factors
- The treatment strategy
Irritable Bowel Syndrome

- Between 7-10% population has IBS¹
- There are 3.6 million physician visits in the U.S. annually for IBS and it consumes over $20 billion in both direct and indirect expenditures²
- Psychiatric disorders occur in 50-60% of patients seeking care for IBS³

Rome III Criteria: IBS

- Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with 2 or more:
  - improvement with defecation
  - onset associated with a change in frequency of stool
  - onset associated with a change in form (appearance) of stool

- Criteria fulfilled in the last 3 months with symptom onset at least 6 months prior to diagnosis

Longstreth et al., Gastroenterology 2006; 130:1480

Pathophysiology

- Altered motility
- Visceral hypersensitivity
- Infection/Inflammation
- Brain-gut axis deregulation
- Brain-gut peptides
Some possible mediators of motility and visceral sensitivity

- **Motility:**
  - serotonin
  - acetylcholine
  - nitric oxide
  - substance P
  - vasoactive intestinal peptide
  - cholecystokinin

- **Visceral sensitivity:**
  - serotonin
  - Tachykinins, bradykinin
  - calcitonin gene-related peptide
  - neurokinin A, NMDA
  - Enkephalins


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Psychosocial Factors

- History of severe physical abuse, sexual abuse, or severe posttraumatic stress disorder strongly influences the severity of symptoms and the clinical outcome1-2

- Other psychosocial factors appear to influence both the decision to seek care3 and also health care utilization by the patient4. These psychosocial factors can be independent predictors of HRQOL5-7

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Current Treatment Strategies for Functional Bowel Disorder

- **Non-pharmacologic**
  - Education and reassurance
  - Dietary advice
  - Lifestyle modification
  - Behavioral modification

- **Pharmacologic**
  - Antispasmodic / anticholinergic
  - Anti-diarrheal
  - Laxatives
  - Antidepressants

Neurotransmitter Imbalance

- Dysregulation of brain-gut neuroenteric system
- Many neurotransmitters, neuromodulators, and neuropeptides are present in both the brain and the gut
- Gastrointestinal homeostasis is dependent on a functional equilibrium between the pathways that enhance and those that inhibit secretion and motility
Neurotransmitter Imbalance

- Serotonergic pathways have been a focus
- Greater than 95% of total body content is found within the gastrointestinal tract
- Intraluminal stimulation of enterochromaffin cells facilitates the release of serotonin (5-HT), which binds to the receptors on the intrinsic and extrinsic afferent neurons, as well as secretory neurons

Mechanisms

- Enhanced perception
- Infectious insults
- Inflammatory processes
- Altered motility
- Visceral hypersensitivity

Adapted from Camilleri and Choi, Aliment Pharmacol Ther 1997; 11:3
**Tricyclic Antidepressants (TCAs)**

- Used in IBS for modulation of hyperalgesia
- Dose for hyperalgesia is typically lower than the dose for depression
- TCAs modulate activity in pain centers in the CNS
- TCAs are anti-cholinergic agents and can induce constipation

**Meta-analysis: TCAs in IBS**

- In a 2009 a meta-analysis of 9 randomized, placebo-controlled trials for functional gastrointestinal disorders with TCAs was performed
- These trials include a total 575 patients
- Relative Risk 0.68 (0.56-0.83)
- Meta-analysis demonstrated symptomatic improvement, NNT = 4

Desipramine vs. Placebo for Moderate to Severe FGIDs

12 week Trial

P=0.16
NNT=8.1

60
47

ITT n=201


Desipramine
Placebo

Desipramine vs. Placebo for Moderate to Severe FGIDs

12 week Trial

P=0.006
NNT=4

73
49

PP n=153


Desipramine
Placebo
## Tricyclic Antidepressants (TCAs)

### Side Effects:

**Anticholinergic**
- Constipation
- Dry Mouth
- Blurred Vision
- Urinary Hesitancy
- Esophageal Reflux

**Central Nervous System**
- Sedation
- Tremor
- Stimulation
- Myoclonic twitches

**Cardiovascular**
- Slowed conduction
- Orthostatic hypotension
- Palpitations
- Hypertension

**Other**
- Weight gain
- Sexual dysfunction
- Impotence
- Perspiration

### Dose Range: 10-200mg

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<th>5-HT</th>
<th>ACh</th>
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Selective Serotonin Reuptake Inhibitors (SSRIs)

• Selectively block the reuptake of 5-HT

• Initially increase availability of 5-HT in synaptic cleft

• Eventually reduce sensitivity of somatodendritic and terminal 5-HT$_{1A}$ autoreceptors

• Increase in neurotrophin expression and enhanced transcription of neurotrophic factors, including BDNF

Meta-analysis: SSRIs in IBS

• In a 2009 a meta-analysis of 5 randomized, placebo-controlled trials for functional gastrointestinal disorders with SSRIs was performed

• These trials only include a total 230 patients

• Relative Risk 0.62 (0.45-0.87)

• Meta-analysis demonstrated symptomatic improvement, NNT = 4

Selective Serotonin Reuptake Inhibitors (SSRIs)

Examples: Citalopram (Celexa)
             Escitalopram (Lexapro)
             Fluoxetine (Prozac)
             Fluvoxamine (Luvox)
             Paroxetine (Paxil)
             Sertraline (Zoloft)

Side Effects: Headache
              GI side effects (nausea, diarrhea, heartburn)
              Sexual dysfunction (↓ libido, delayed orgasm)
              Sleep disturbance (insomnia, somnolence)

Dose Range: 10-100mg

SSRIs and TCAs: Synergy

• Enhance effectiveness of endogenous pain inhibition and modulate hyperalgesia

• Both SSRIs and TCAs may be equally effective in improving IBS symptoms

• Reported success of combination of SSRIs with TCAs for pain modulation if one alone is insufficient

Choosing an Antidepressant (ACG)

- TCAs and SSRIs are more effective than placebo at relieving global IBS symptoms, and appear to reduce abdominal pain.
- There are limited data on the safety and tolerability of these agents in patients with IBS.
- Diarrhea – TCA
- Constipation – SSRI


Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

**Examples:** Desvenlafaxine (Pristiq)
Venlafaxine (Effexor)
Duloxetine (Cymbalta)
Milnacipran (Savella) – “Fibromyalgia”

**Side Effects:** Same as SSRIs PLUS:
- potential treatment-emergent HTN
- tachycardia
Comparison of Agents

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Mirtazapine

**Mechanism of Action**

- $\alpha_2$-adrenergic receptor antagonist
- 5-HT$_2$, 5HT$_3$ receptor antagonist
- Potent H$_1$ receptor antagonist

**Side Effects**

- Dry Mouth
- Somnolence
- Sedation
- Weight Gain
Anxiolytics

- Benzodiazepines - limited anecdotal evidence of possible benefit
- Limited evidence even in pts with co-occurring anxiety disorder
- Addiction potential, worsening of associated depression, and poor safety profile make them less than attractive candidates


Psychological Treatments

- Collaborative treatment of psychological symptoms with gastroenterology and psychologists has demonstrated improvements in medical symptoms and global self assessment

Gerson CD, Gerson MD. A Collaborative Health Care Model for the Treatment of Irritable Bowel Syndrome. Clinical Gastroenterology and Hepatology. 2003;1:446-452
Psychological Treatment

- **Cognitive Behavioral Therapy** – (CBT) seven studies done comparing CBT to “control” or usual treatment. Total patients = 493

- IBS symptoms persisted in 118 of 279 assigned to CBT or 42.3%. IBS symptoms persisted in 130 of 212 of those assigned to usual care or 61.3%

- NNT = 3


Psychological Treatments

- **Hypnotherapy** – 2 small studies, N=40. symptoms persisted in 15/20 (75%) of the “controls” and 7/20 (35%) of the hypnotherapy patients with a NNT of 2

- **Relaxation therapy** – 5 studies, N=234. symptoms persisted in 100/112 of the “controls” (89.3%) and 94/192 (77.0%) of the relaxation therapy patients

- **Psychodynamic psychotherapy** – 2 studies, N=273. symptoms persisted in 95/135 (70.4%) “controls” and 61/138 (44.2%) of the therapy patients with a NNT of 3.5

Behavioral Therapy

- Includes biofeedback, relaxation therapy, cognitive behavioral therapy, dynamic psychotherapy and hypnotherapy
- Relaxation therapy NOT effective
- Grade B RCTs (poorly blinded) indicate improvement in GI and psychological symptoms in pts with co-morbid psychiatric diagnosis
- Designs are inferior to drug trials

Benefits of Collaboration

- Increased time with a team of physicians
- Thorough assessment of psychosocial factors
- Expanded treatment plan to include psychotropics commonly used in IBS that are dosed based on patient-specific factors as well as psychotherapy
- Potential to decrease visits to GI Clinic and Emergency Services
Summary

• The exact pathophysiology of IBS is multifactorial and incompletely understood

• Carefully selected psychotropic medication can be useful in patients with IBS

• Choosing a psychotropic is improved with a understanding of physiology and knowledge of side effect profiles