Psychopharmacology for the Gastroenterologist

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Rationale for Antidepressants

- Treatment of psychiatric comorbidity
- Peripheral effects
  - Motility/secretion
  - Afferent
- Central pain modulatory effects
Psychiatric Comorbidity in IBS


Subjects with diagnosis (%)

0  25  50  75  100

- Anxiety disorders
- Affective disorders
- Somatization disorder
- Other disorders
- Any psychiatric disorder

= range and weighted mean
IBS - Antidepressants

NE=norepinephrine; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant
Response to Noxious Colorectal Distension in Rats

CNS Contribution to GI Pain

- Functional Abdominal Pain (FAPS)
- Functional GI disorders
  - IBS
  - Functional dyspepsia
- Chronic GI disorders
  - GERD
  - IBD
- Acute GI episodes
  - Bowel obstruction
  - Cholecystitis

Visceral Hypersensitivity in IBS, But Not FAPS

Perceptual Threshold (mmHg)

Discomfort          | Pain          | Maximum
---                  | ---          | ---
FAPS                 | IBS          | Control

FAPS=functional abdominal pain
IBS: Brain-Gut Influences on Severity and Treatment

- Injury
- Infection
- Diet
- Hormones, Peptides

Afferent excitation

Mild

Moderate

Severe

Life stress
Psych Dx
Poor coping
Abuse

Diet
Gut medications
Antidepressants
Behavioral Rx
Lifestyle

IBS - Ascending Visceral Pain Pathway

Descending Visceral Pain Pathway

Increased dACC in IBS Consistent with Greater Affective Pain Experience

55 mm Hg of Distension

45 mm Hg of Distension

dACC=dorsal anterior cingulate cortex

Severe IBS / Psychological Distress

Clinical Recovery (8 months later)

BA = Broca’s area; MCC = Mid Cingulate Cortex; SI = Somatosensory cortex; Ant Ins = Anterior Insula
IBS + Abuse vs Others (50 mm Hg)

PCC, MCC, sACC = areas of the brain associated with visceral and sensory reception emotion and pain regulation. We are looking at how they are activated before and after clinical improvement. Ringel Y et al. *Gastroenterology.* 2008;134:396-404.
Effects of Amitryptyline on Reducing Global Brain Activation with Rectal Pain and Psychological Stress

ACC=anterior cingulate cortex

Posterior Parietal Cortex
Perigenual ACC
### Overall Forest Plot of Antidepressant Studies

#### Tricyclic Antidepressants (TCAs)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control n/N</th>
<th>RR (random)</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heefner, 1978</td>
<td>10/22</td>
<td>12/22</td>
<td>5.94</td>
<td>0.83 (0.46, 1.51)</td>
</tr>
<tr>
<td>Myren, 1982</td>
<td>5/30</td>
<td>10/31</td>
<td>2.66</td>
<td>0.52 (0.20, 1.33)</td>
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<tr>
<td>Ngain, 1984</td>
<td>14/21</td>
<td>21/21</td>
<td>14.74</td>
<td>0.67 (0.49, 0.90)</td>
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<tr>
<td>Boerner, 1988</td>
<td>16/42</td>
<td>19/41</td>
<td>7.63</td>
<td>0.82 (0.30, 1.36)</td>
</tr>
<tr>
<td>Bergmann, 1981</td>
<td>5/19</td>
<td>14/16</td>
<td>3.82</td>
<td>0.30 (0.14, 0.65)</td>
</tr>
<tr>
<td>Vil, 1991</td>
<td>14/25</td>
<td>20/25</td>
<td>10.67</td>
<td>0.70 (0.47, 1.04)</td>
</tr>
<tr>
<td>Drossman, 2003</td>
<td>60/115</td>
<td>36/37</td>
<td>16.77</td>
<td>0.83 (0.63, 1.08)</td>
</tr>
<tr>
<td>Talley, 2008</td>
<td>0/18</td>
<td>5/16</td>
<td>0.33</td>
<td>0.08 (0.00, 1.36)</td>
</tr>
<tr>
<td>Vahedi, 2008</td>
<td>8/27</td>
<td>16/27</td>
<td>5.02</td>
<td>0.50 (0.26, 0.97)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>319</strong></td>
<td><strong>256</strong></td>
<td><strong>67.36</strong></td>
<td><strong>0.68 (0.56, 0.83)</strong></td>
</tr>
</tbody>
</table>

Total events: 32 treatments; 153 controls
Test for heterogeneity: Chi2=10.94, df=8, (P=0.21), F=26.9% 
Test for overall effect: Z=3.86 (P=0.0001)

\n
n=number of patients with persistent or unimproved symptoms; N=total number of patients treated
Abuse, FGIDs and other chronic pain conditions are associated with reduced neuronal density in brain pain control areas.

Antidepressants and psychological treatments may reverse this process and regrow neurons → neurogenesis.

- May occur in brain and intestines.

Augmentation, ie, use of low dose combinations of medications and psychological treatments appear to improve the treatment response for longer periods of time.

References:
Altered Brain Structure in IBS

Cortical Thinning in Anterior MCC

MCC=midcingulate cortex
Correlation of Cortical Thickness with Daily Pain Scores (VAS) in Painful Chronic Pancreatitis

VAS=visual analog scale
Cortical Thickness of Pain Control Areas: Painful Chronic Pancreatitis vs. Controls

VAS=visual analog scale
Neurogenic Theory of Depression and Antidepressant Treatment

Genes and early life stress

Dentate neuron vulnerability

Social stress, drug abuse, medical illness

Antidepressants, Psychological treatment

Trigger

Critical threshold leading to depression

Uncoupling of affect from context

Dentate neurons

Basal neurogenesis

Suppressed neurogenesis

Restored neurogenesis

BDNF=brain-derived neurotrophic factor.
Augmentation Treatment for Refractory FGIDs

- 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
- Beginning to use with refractory GI disorders
- Examples
  - Add buspirone or bupropion to antidepressant
  - SSRI and TCA
  - Add atypical antipsychotic (eg, quetiapine) to TCA or SNRI
  - Mood stabilizer (eg, lamotrigine) to antidepressant
  - Combine antidepressant and psychological treatment
IBS - Psychotropic Agents

• Antidepressants
  – Tricyclics (TCAs)
  – Selective serotonin reuptake inhibitors (SSRIs)
  – Serotonin/norepinephrine reuptake inhibitors (SNRI’s)
  – Other agents: mirtazapine, nefazadone, buproprion

• Anxiolytics
  – Benzodiazepines
  – Azapirones (buspirone)

• Antipsychotics
  – Phenothiazines (eg, chlorpromazine)
  – Butyrophenones (eg, haloperidol)
  – Atypicals (eg, quetiapine, olanzapine, risperidone)

• Mood stabilizers
  – Lithium
  – Anticonvulsants (eg. valprioc acid, carbamazepine)
  – Lamotrigine
# Antidepressant Receptor Site Effects

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

## SSRIs (1-2 pills)

<table>
<thead>
<tr>
<th></th>
<th>5HT</th>
<th>Histamine</th>
<th>Ach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>+++</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>+++</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>+++</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>+++</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>Sertraline</td>
<td>+++</td>
<td>nil</td>
<td>nil</td>
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</table>

## SNRI’s (variable)

<table>
<thead>
<tr>
<th></th>
<th>5HT</th>
<th>Histamine</th>
<th>Ach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine</td>
<td>++</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>+++</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>+++</td>
<td>nil</td>
<td>nil</td>
</tr>
</tbody>
</table>

# Antidepressant Treatment

<table>
<thead>
<tr>
<th></th>
<th>TCA</th>
<th>SSRI</th>
<th>SNRI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potential benefits</strong></td>
<td>Pain depression</td>
<td>(pain) depression, panic, anxiety, OCD</td>
<td>pain depression</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>Sedation, Hypotension, Constipation, Dry mouth/eyes, Arrhythmias, Weight gain, Sex dysfunction</td>
<td>Insomnia, Agitation, Diarrhea, Night sweats, Headache Weight loss, Sex dysfunction</td>
<td>Nausea, Agitation, Dizziness, Sleep disturbance, Fatigue Liver dysfunction</td>
</tr>
<tr>
<td><strong>Risk from overdose</strong></td>
<td>moderate</td>
<td>minimal</td>
<td>minimal</td>
</tr>
<tr>
<td><strong>Efficacy for IBS</strong></td>
<td>good</td>
<td>not studied</td>
<td>good?</td>
</tr>
<tr>
<td><strong>Dose Adjustment</strong></td>
<td>yes</td>
<td>not usual</td>
<td>varies</td>
</tr>
<tr>
<td><strong>Cost / month</strong></td>
<td>$5-30</td>
<td>$40-80</td>
<td>$60-100</td>
</tr>
</tbody>
</table>

Other Central Agents with GI effects

- **Mirtazepine**
  - Serotonergic and noradrenergic drug with $5HT_2$ and $5HT_3$ effects – can have pain benefit
  - Use with nausea, anorexia, weight loss, diarrhea
  - Some sedation

- **Clonidine**
  - $\alpha_2$-adrenergic against with central (anxiety reduction) and peripheral (pain reduction via bowel compliance)
  - Helps reduce diarrhea
  - Prevents adrenergic effects of narcotic withdrawal

- **Buspirone**
  - Azapirone with anti-anxiety effects acting on non BZD GABA receptors
  - Has $5HT_1$ and $5HT_2$ effects
  - Potential benefit for PDS (dyspepsia) due to receptive relaxation of stomach

Quetiapine
- Atypical antipsychotic with complex effects
- Dopamine (D$_1$ and D$_2$) and Serotonin (5HT$_{1a}$ and 5HT$_2$) antagonism with some α2-adrenergic blocking effect

Treatment Effects
- Bipolar disorder and schizophrenia (labelling)
- Augment OCD, PTSD, restless legs, autism, tourettes or other antidepressants
- Sleep (normal sleep architecture)
- Anxiety reduction
- Some analgesic benefit

Side effects
- Sedation, somnolence, dry mouth
- Metabolic syndrome (weight gain, glucose intolerance, hyperlipidemia)
- Abnormal LFTs (rare)
Augmentation Therapy

- Two different antidepressants
- Antidepressant + non-pharmacological Rx
- Antidepressant + atypical antipsychotic
- Antidepressant + anticholinergic
- Antidepressant + pregabalin or gabapentin

Dynamic-interpersonal psycho Rx

Cognitive behavioral Rx

Hypnosis

Antidepressants

Symptomatic Rx

Non-pharmacologic Rx

Pharmacologic Rx

Patient-physician Therapeutic relationship
Patient with frequently recurring painful IBS

You recommend an antidepressant

The patient promptly states:

“The doctor before you gave me an antidepressant . . . it made me sleepy and didn’t work. Besides, I don’t want something that alters my mind.”
Physician - Patient Relationship

Insert Antidepressant Video Here
Approach to Prescribing Antidepressants

• Address false beliefs or expectations of patients
  – “You think I’m crazy / depressed?”
  – “It will alter my mind”
  – “It’s addicting”
  – “I’ve tried them - made me sick (didn’t work)”

Approach to Prescribing Antidepressants

- Address false beliefs or expectations of patients
- Provide information / rationale consistent with patient interests
  - Central analgesic - neuromodulator
  - Lower doses than for therapy of depression
  - Not addicting
  - No carry over effects with discontinuation

Gate Control Theory

- Pain
- Midbrain
- Spinal Cord
- Intestinal Afferent Receptor
- Inhibitory Pathway
- Pain Gate
Approach to Prescribing Antidepressants

- Address false beliefs or expectations of patients
- Provide information / rationale consistent with patient interests
- Negotiate a treatment plan
  - Benefit occurs in 4-6 weeks
  - Most side effects diminish in 1-2 weeks
  - Plan to mutually discuss dose range options
  - Consider previous drugs that worked

Approach to Prescribing Antidepressants

- Address false beliefs or expectations of patients
- Provide information / rationale consistent with patient interests
- Negotiate a treatment plan
- Continue dialog for 4-6 weeks
  - Phone call first week is critical
  - Assess compliance
  - Involve patient in treatment decisions
  - Gauge response by behaviors and function
  - If side effects:
    - First reduce dose
    - May switch within same class

If Poor Initial Response, Consider . . .

- Re-address patient concerns
- Consider a psychiatric consultation for pharmacotherapy
- Switch to different class of drug
- Combination therapies
  - SSRI and low-dose TCA
  - TCA or SSRI and buspirone
  - Antidepressant and psychological treatment

Combing Antidepressants + Psych Treatments

- **Clinical Observations**
  - Antidepressants improve pain, vegetative signs and hopelessness, and increase motivation for psych treatments
  - Psychological treatments improve coping, cognitive function, and effects of trauma, and increase adherence to medication

- **Brain Imaging**
  - Antidepressants may have “bottom up” effects, acting on paralimbic (cingulate, insula)
  - Psychological treatments may have “top down” effects on prefrontal cognitive areas improving “executive” function

- **Clinical trials show combined treatments > monotherapy for headache, depression and other psych disorders**
IBS - Treatment

Patient - Physician Relationship

* Monitor side effects
IBS - Treatment

Severity

Symptomatic medical treatment
Stress reduction
Exercise, yoga, etc.

Patient - Physician Relationship

* Monitor side effects
IBS - Treatment

**Patient - Physician Relationship**

- Symptomatic medical treatment
  - Stress reduction
  - Exercise, yoga, etc.

**Psychiatric referral**

- Low dose TCA or SNRI or SSRI
  - 4-6 wks*
- Increase dose
  - 4-6 wks*
- Augmentation
  - “2 drugs”
  - 4-6 wks*

**Mental health referral**

- CBT
- Hypnosis
- IP psychotherapy
- Stress management

**Severity**

* Monitor side effects
IBS - Treatment

Patient - Physician Relationship

Symptomatic medical treatment
Stress reduction
Exercise, yoga, etc.

* Monitor side effects

Severity

Psychiatric referral

Combined AD + psych

Augmentation “2 drugs”
4-6 wks*
Increase dose
4-6 wks*
Low dose TCA or SNRI or SSRI

CBT
Hypnosis
IP psychotherapy
Stress management

Mental health referral

* Monitor side effects