Antidepressants in IBS

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Antidepressants – Rationale for Use in IBS

- Effective in chronic pain (TCA > SSRIs)
- Reduction in pain is independent of their effects on mood
- Are effective in conditions that overlap with IBS (eg, fibromyalgia, interstitial cystitis)

Potential Sites of Action of Antidepressants in IBS

Antidepressant action

Visceral analgesia

Changes in motility

Smooth muscle relaxation

Adapted from Rome Foundation Functional GI Disorders Specialty Modules.
## Efficacy of TCAs in Relieving Global IBS Symptoms

### Study (Year, Drug, Dose) | Treatment n/N | Control n/N | RR (Random) 95% CI
---|---|---|---
Heefner (1978, desipramine 150 qd) | 10/22 | 12/22 | 0.68 (0.56-0.83)
Myren (1982, trimipramine 50 qd) | 5/30 | 10/31 | 0.56 (0.35-0.90)
Nigam (1984, amitriptyline 12.5 qd) | 14/21 | 21/21 | 0.64 (0.42-0.97)
Boerner (1988, doxepin 50 qd) | 16/42 | 19/41 | 0.82 (0.52-1.31)
Bergmann (1991, trimipramine 50 qd) | 5/19 | 14/16 | 0.38 (0.17-0.87)
Vij (1991, doxepin 75 qd) | 14/25 | 20/25 | 0.68 (0.41-1.09)
Drossman (2003, desipramine 50-150 qd) | 60/115 | 36/57 | 0.68 (0.56-0.83)
Talley (2008, imipramine 50 qd) | 0/18 | 5/16 | 0.20 (0.02-1.64)
Vahedi (2008, amitriptyline 10 qd) | 8/27 | 16/27 | 0.50 (0.29-0.88)
Subtotal (95% CI) | 319 | 256 | 0.68 (0.56-0.83)

*Significant heterogeneity among studies may limit conclusions.
Study duration ranged from 4 weeks to 3 months.
Amitriptyline in IBS-D

54 pts with Rome II IBS-D
Amitriptyline 10 mg vs placebo
For 2 months
Amitriptyline improved:
incidence of loose stools
feeling of incomplete evacuation
Loss of all symptoms
AE similar between groups

Figure 2. Daily changes in number of symptoms of Patients in drug and placebo groups.
Desipramine in IBS and Other Functional Bowel Disorders

Desipramine demonstrated marginal benefit in patients with diarrhea-predominant stool form (n=32, P=0.08).

*Study population included patients with IBS, functional constipation, chronic functional abdominal pain, and unspecified functional bowel disorders. 26% of patients d/c despramine secondary to SEs (e.g., constipation, fatigue)

ITT=intent to treat; PP=per protocol.
Response=satisfaction with treatment; response to an 8-item questionnaire.

Tricyclic Antidepressants Side Effects

Tertiary Amines
- Amitriptyline
- Imipramine
- Doxepin
- Trimipramine

Secondary Amines
- Nortriptyline
- Desipramine

Receptor Affinity
- Acetylcholine
- Histamine$_1$
- a$_1$-adrenergic

# Efficacy of SSRIs in Relieving Global IBS Symptoms*

<table>
<thead>
<tr>
<th>Study</th>
<th>(Year, Drug, Dose)</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (Random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuiken</td>
<td>(2003, fluoxetine 20 qd)</td>
<td>9/19</td>
<td>12/21</td>
<td>RR = 0.62 (95% CI=0.45-0.87)</td>
</tr>
<tr>
<td>Tabas</td>
<td>(2004, paroxetine 10-40 qd)</td>
<td>25/44</td>
<td>36/46</td>
<td></td>
</tr>
<tr>
<td>Vahedi</td>
<td>(2005, fluoxetine 20 qd)</td>
<td>6/22</td>
<td>19/22</td>
<td></td>
</tr>
<tr>
<td>Talley</td>
<td>(2008, citalopram 40 qd)</td>
<td>5/17</td>
<td>5/16</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>(95% CI)</td>
<td>113</td>
<td>117</td>
<td></td>
</tr>
</tbody>
</table>

*Significant heterogeneity among studies may limit conclusions. Study duration ranged from 6 weeks to 12 weeks.

Fluoxetine in IBS with Constipation

Treatment period was 12 weeks

- At week 4, all symptoms evaluated (bloating, discomfort, stool consistency, change in bowel habit <3 bowel movements / week) less frequent in the fluoxetine patients vs placebo (p<0.05)
- Mean number symptoms per patient decreased from 4.6–0.7 in fluoxetine patients vs 4.5–2.9 in control patients (p<0.001)
- Low dose fluoxetine effective in IBS patients, but there is need for further studies
- Fluoxetine is not FDA approved in IBS

Vahedi et al, Aliment Pharmacol Ther 2005; 22: 381
Antidepressants in IBS

- 51 IBS (mostly IBS-D)
- RDBPC; 12 weeks
  - Impramine 50 mg
  - Citalopram 40 mg
  - Placebo
- No difference in global assessments or abdominal pain
- Imipramine 50 mg improved depression score and SF-36 Mental Component score

Table 2 Change scores on treatment and placebo

<table>
<thead>
<tr>
<th>Variable (ITT analysis)</th>
<th>Citalopram (n = 17)</th>
<th>Imipramine (n = 18)</th>
<th>Placebo (n - 16)</th>
<th>Variance explained (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate relief (last week of therapy,%)</td>
<td>69.2</td>
<td>100</td>
<td>69.2</td>
<td>1</td>
<td>0.80</td>
</tr>
<tr>
<td>CGI (mean, SD)</td>
<td>-0.2 (1.5)</td>
<td>-0.7 (1.1)</td>
<td>-0.6 (1.5)</td>
<td>3</td>
<td>0.60</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>-14.4 (32.9)</td>
<td>-45.3 (26.3)</td>
<td>-7.4 (46.9)</td>
<td>18</td>
<td>0.10</td>
</tr>
<tr>
<td>BSSRS frequency</td>
<td>-3.5 (5.3)</td>
<td>-4.7 (5.2)</td>
<td>-4.4 (7.0)</td>
<td>1</td>
<td>0.80</td>
</tr>
<tr>
<td>BSSRS distress</td>
<td>-2.7 (4.4)</td>
<td>-7.2 (6.5)</td>
<td>-2.5 (6.3)</td>
<td>13</td>
<td>0.05</td>
</tr>
<tr>
<td>BSSRS disability</td>
<td>-3.5 (4.6)</td>
<td>-7.7 (6.4)</td>
<td>-1.2 (6.0)</td>
<td>18</td>
<td>0.03</td>
</tr>
<tr>
<td>HADS anxiety</td>
<td>1.1 (2.0)</td>
<td>2.0 (1.7)</td>
<td>0.6 (1.3)</td>
<td>12</td>
<td>0.20</td>
</tr>
<tr>
<td>HADS depression</td>
<td>0.3 (1.3)</td>
<td>-10.0 (0.9)</td>
<td>-0.6 (1.6)</td>
<td>17</td>
<td>0.08</td>
</tr>
<tr>
<td>SF-36 physical</td>
<td>3.5 (6.1)</td>
<td>7.3 (7.3)</td>
<td>6.5 (4.6)</td>
<td>8</td>
<td>0.40</td>
</tr>
<tr>
<td>SF-36 mental</td>
<td>-0.0 (4.1)</td>
<td>4.8 (4.5)</td>
<td>-1.9 (7.2)</td>
<td>23</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Data are presented as changes in the scores from baseline to endpoint; negative scores indicate a decrease from baseline.
A ITT, Intention-to-treat; CGI, Clinical Global Impressions Scale; BSSRS, Bowel Symptom Severity Rating Scale; HADS, Hospital Anxiety And Depression Scale

Talley, et al. DDS, 2008
SSRI Side Effects

- Citalopram
  - side effects include: nausea/dry mouth, vomiting, excessive sweating, HA, tremors, inability to sleep, sexual dysfunction, withdrawal reaction

- Fluoxetine
  - Fewer withdrawal effects

- Paroxetine
  - Greatest anticholinergic effect of SSRIs

_Drossman et, al., Gastro, 2002; 123:2108_
Approach to Prescribing Antidepressants in IBS

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

• Discuss mechanism of action:
  – Central analgesic
  – Lower doses than for therapy of depression
  – Not addicting
  – No carry over effects with discontinuation

Drossman et al., Gastro, 2002; 123:2108
Approach to Prescribing Antidepressants in IBS

Choice of Antidepressant will depend on:
Symptoms (eg. pain, diarrhea, constipation)
Side effects

Remember:
- Benefit occurs in 4-6 weeks
- Most side effects diminish in 1-2 weeks
- Consider previous drugs that worked

Drossman et al., Gastro, 2002; 123:2108
Antidepressants – Tips for improving Effectiveness

- Inform patients of expected AE (e.g. sedation, agitation)
- Start with a low dose; often will need to reach 50-75 mg QD for TCAs for efficacy
- Consider switching if not effective or SEs
- Use AE profiles to help select agents

Clouse, Gastroenterology, 1999
An algorithm for the initiation of antidepressants in irritable bowel syndrome (IBS).

IBS diagnosis

Moderate to severe or Refractory symptoms

Somatisation disorder suspected?

YES

Initiate very low dose TCA regimen

Consider non-pharmacological therapy for intolerance or poor response

Initiate contemporary antidepressant at usual dose

Monitor symptom response and add low dose TCA for persistent IBS symptoms

NO

Active anxiety or affective disorder present

Initiate very low dose TCA regimen

NO evidence for active anxiety or affective disorder

Initiate very low dose TCA regimen

Monitor symptom response and add contemporary antidepressant for persistent psychiatric symptoms

*Clouse R E Gut 2003;52:598-599
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| Antidepressants | | |
|-----------------|-----------------|
| **TCAs:** more effective than placebo at relieving global IBS symptoms and appear to reduce abdominal pain. There is limited data on safety and tolerability in IBS | Grade 1B |
| **SSRIs:** more effective than placebo at relieving global IBS symptoms and appear to reduce abdominal pain. There is limited data on safety and tolerability in IBS | Grade 1B |