Drug treatment of Irritable Bowel Syndrome:
Different approaches for different subtypes
IBS patients are very heterogeneous!
Changing fashions in IBS treatment
Targeting the Gut or the Brain?


Gut

- mebeverine
- ispaghula
- Tegaserod
- Probiotics
- Prebiotics
- Antibiotics
- Linaclotide
- Lubiprostone
- 5HT3 antagonists

Brain

- Tricyclic antidepressants
- SSRIs
- Dextofisopam
- Cognitive behavioural therapy
- Hypnosis
What is IBS?

• Loose definition
  – Abdominal pain / discomfort with disturbed bowel habit in absence of organic disease

• Stricter diagnostic criteria
  – Rome I/ II & III
Rome III
Diagnostic Criteria for IBS*

- Recurrent abdominal pain or discomfort
  \( \geq 3 \text{ days per month in the last three months} \)
- associated with two or more of the following
  - Improvement with defecation; \textit{and/or}
  - Onset associated with a change in frequency of stool; \textit{and/or}
  - Onset associated with a change in form (appearance) of stool

* Criteria fulfilled for the last 3 months with symptom onset \( \geq 6 \text{ months} \) prior to diagnosis
Most bothersome symptoms in subtypes of IBS

Tillisch Am J Gastroenterol 2005;100:896-904
Visceral hypersensitivity in 50% of IBS

Mertz et al Gastroenterology 1995
Where does your patient fit in the multidimensional IBS space?

Visceral hypersensitivity

Pain

Somatisation

Non colonic features

Constipation

Bowel habit

Diarrhoea
How to identifying those in whom therapy should be directed at the brain?
Multiple somatic symptoms distinguish IBS from Organic disease in Primary Care

<table>
<thead>
<tr>
<th>Symptom</th>
<th>IBS (%)</th>
<th>Organic (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysymptomatic</td>
<td>46</td>
<td>24</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>Previous unexplained symptoms</td>
<td>46</td>
<td>17</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Thompson et al 2000
IBS as a presentation of “somatisation”

Somatization disorder

Physical symptom disorder

North et al  Clin Gastroenterol Hepatol 2004;2(9):787-95
“Physical symptom disorder”

- One or more physical symptoms
- Not fully explainable by another medical or psychiatric disorder
- Duration > 6 months

Kroenke J Psychosom Res 2006;60(4):335-9
<table>
<thead>
<tr>
<th>Personal Health Questionnaire-15 (PHQ-15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>During the past 4 weeks, how much have you been bothered by any of the following problems?</td>
</tr>
<tr>
<td>Stomach pain</td>
</tr>
<tr>
<td>Back pain</td>
</tr>
<tr>
<td>Pain in your arms, legs, or joints (knees, hips, etc)</td>
</tr>
<tr>
<td>Menstrual cramps or other problems with your periods (Women only)</td>
</tr>
<tr>
<td>Headaches</td>
</tr>
<tr>
<td>Chest pain</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Symptom</td>
</tr>
<tr>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>Fainting spells</td>
</tr>
<tr>
<td>Feeling your heart pound or race</td>
</tr>
<tr>
<td>Shortness of breath</td>
</tr>
<tr>
<td>Pain or problems during sexual intercourse</td>
</tr>
<tr>
<td>Constipation, loose bowels, or diarrhoea</td>
</tr>
<tr>
<td>Nausea, gas, or indigestion</td>
</tr>
<tr>
<td>Feeling tired or having low energy</td>
</tr>
<tr>
<td>Trouble sleeping</td>
</tr>
</tbody>
</table>
Severity of somatic symptom burden

PHQ-15 scores
- Mild = 5–9
- Moderate = 10–14
- Severe = ≥15

Excluding GI symptoms

PHQ-12 scores
- Mild = 4–7
- Moderate = 8–11
- Severe = ≥12
Somatization accounts for excess psychiatric disease in IBS

North et al. Clin Gastroenterol Hepatol 2004 Sep;2(9):787-95
Somatisation predicts behaviour of FGIDs

- 53 IBS patients from OP clinic
- SD found in 25%

SD patients
  - 2X incidence of other functional GI disorders
  - Less likely to report marked treatment response
    • 0% SD versus 46% non SD

- More health care utilisation
  - Phone calls, ER visits, MDs consulted, days off work

Mechanism of somatisation

- Abnormal CNS pain processing of peripheral stimuli
- Common theme in
  - Fibromyalgia
  - Temporo-mandibular joint dysfunction
  - Functional dyspepsia
  - Functional heartburn
  - IBS
Treatment of Somatisation disorder

• Difficult!
  – Locally acting treatments futile
  – Antidepressants- SSRIs
  – Cognitive Behavioural Therapy
How to treat those without somatisation?

Distribution of severity of “physical symptom disorder”

- Severe
- Moderate
- Mild / none

• Predominant IBS symptom
  - IBS with diarrhoea (IBS-D)
  - IBS with constipation (IBS-C)
  - IBS with mixed / alternating bowel habit (IBS-M, IBS-A)
  - IBS with bloating
IBS-D

• Diet
  – Avoid dietary excesses
    • Especially wheat bran, alcohol, caffeine
  – Reduce FODMAPs (Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols)
    • fructo-oligosaccharides (fructans) and galactooligosaccharides (raffinose), lactose, fructose, sorbitol, mannitol
Sources of substantial amounts of fructose in diet (>3gm / portion)

- Fruit: apples, pear, melon, cherry, lychee
- Concentrated fruit juice
- Dried fruit: currant, sultana, date, fig, prune
- Sweeteners in soft drinks
  - High fructose corn starch
- Sauces
### Sources of fructans in diet

<table>
<thead>
<tr>
<th>Food</th>
<th>Serving size (g)</th>
<th>Fructan content g</th>
</tr>
</thead>
<tbody>
<tr>
<td>White bread</td>
<td>2 slices (65 g)</td>
<td>1.8</td>
</tr>
<tr>
<td>Pasta</td>
<td>(165 g)</td>
<td>2.5</td>
</tr>
<tr>
<td>Wholemeal cereal</td>
<td>(60 g)</td>
<td>1.9</td>
</tr>
<tr>
<td>Biscuit</td>
<td>2 biscuits (40 g)</td>
<td>1.2</td>
</tr>
<tr>
<td>Onion</td>
<td>(35 g)</td>
<td>2.1</td>
</tr>
<tr>
<td>Leek</td>
<td>(85 g)</td>
<td>5.6</td>
</tr>
<tr>
<td>Asparagus</td>
<td>6 spears (90 g)</td>
<td>2.6</td>
</tr>
<tr>
<td>Jerusalem artichoke</td>
<td>(75 g)</td>
<td>15</td>
</tr>
</tbody>
</table>
Low FODMAP diet for IBS

62 IBS patients given advice on low FODMAP diet + 1 hour education, advice on fructose / fructan content of food
Telephoned at 14(2-40 months)

Shepherd et al  J Am Diet Assoc 2006;106:1631-1639
Other treatments for IBS-D

• Loperamide
  – Small trials
  – Most show control of diarrhoea
  – Around 50% improvement of pain / discomfort

• 5HT₃ antagonists
  – Alosetron / Cilansetron
    • Large well designed trials
    • Clear benefit for stool consistency
    • ↓ urgency, ↓ pain
    • ↑% responders “satisfactory relief of symptoms”
    • Number needed to treat (NNT) = 7
    • Withdrawn owing to “ischemic colitis”
Treatment of IBS-C

• Bulking agents
  – Ispaghula
    • Prior et al Gut 1987;28:1510-1513
  – Bran ineffective in secondary care at least
    • Snook et al Aliment Pharmacol Ther 1994;8:511-514

• Prokinetics: 5HT$_3$ and 5HT$_4$ agonists
  – MCK-733
  – (Tegaserod) NNT=14
    • Evans et al Cochrane Database Syst Rev 2004;CD003960
  – Prucalopride
    • Sloots et al Aliment Pharmacol Ther 2002;16:759-767
Effect of 5HT$_4$ agonist on bowel function in C-IBS

Bowel frequency / week

Stool consistency

Tegaserod 2mg/6mg bd

Placebo

Novel agents for constipation

- **Lubiprostone**
  - Prostaglandin E1 analogue
  - Activates chloride channels stimulating secretion
  - Accelerates small bowel and colonic transit
  - Delays gastric emptying
  - Nausea at higher doses
Lubiprostone for IBS-C?

- RCT of Lubiprostone 16, 32 & 48 ug/day in 195 IBS-C patients
- ↓ abdominal pain at month 1&2
- ↓ constipation, ↑ spontaneous BM & ↓ stool consistency
- No difference in % responders (“satisfactory relief”)

Change in spontaneous bowel movements / week

Johanson et al  Aliment Pharmacol Ther 2008;27:685-696
Linaclotide

• Novel oral guanylate cyclase C agonists
• Mimics the natural secretagogue guanylin.
• Stimulates chloride secretion acting via enterocytes receptor guanylate cyclases
• $\uparrow$ cyclic cGMP $\rightarrow$ chloride secretion
• Softens stool and eases stool passage
Linaclotide in IBS-C

- 36 IBS-C patients
- 5 days of Placebo, Linaclotide 100 μg, Linaclotide 1000 μg all n = 12

Andresen et al  Gastroenterology 2007;133:761-768
Treatment of IBS-mixed

- Limited data
- Antispasmodics
  - Mebeverine
- Tricyclics
  - Amitriptyline
  - Paroxetine
  - Dextofisopam
Dextofisopam

- 2,3-benzodiazepine receptor agonist
- Bind to subcortical regions including hypothalamus
- Less sedating and less motor impairment than diazepam
  (1,5-benzodiazepine receptor agonist)
Dextofisopam in IBS-D & IBS-A
% with adequate relief

Leventer et al  Aliment Pharmacol Ther 2008;27:197-206
Bloating

- With visible abdominal distension
  - Linked to constipation
    • Houghton et al. Gastroenterology 2006;131:1003-1010

- Without visible distension
  - Linked to visceral hypersensitivity
    • Agrawal et al. Gut 2007;56:A62
Ambulatory abdominal inductance plethysmography

- Validated measure of abdominal girth

Lewis et al. Gut 2001;48:216-220
Bloating & distension in IBS

- 20 IBS-C
- 20 IBS-D
- 10 IBA-A
- 24 hour ambulatory girth measurement

Houghton et al  Gastroenterology 2006;131:1003-1010
24 hour profile of abdominal girth in health & IBS

Houghton et al. Gastroenterology 2006;131:1003-1010
Change in girth in IBS vs healthy volunteers

- IBS tend to show maximum girth towards end of day
- Worse for IBS-C

Houghton et al. Gastroenterology 2006;131:1003-1010
Treatment for bloating

• With abdominal distension
  – Treat constipation
    • Prokinetics (Tegaserod)
  – Probiotics?
  – Rifaximin?

• Without visible distension
  – Likely visceral hypersensitivity--Tricyclics
<table>
<thead>
<tr>
<th>Probiotic</th>
<th>n</th>
<th>Duration</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>L. plantarus</em></td>
<td>60</td>
<td>4 weeks</td>
<td>Flatulence ↓</td>
<td>Nobaek 2000</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td></td>
<td></td>
<td>Niedzielin 2001</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td></td>
<td>Global symptoms ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>70</td>
<td></td>
<td>NS</td>
<td>Sen 2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pain ↓</td>
<td>Saggioro 2004</td>
</tr>
<tr>
<td>VSL#3</td>
<td>25</td>
<td>4 weeks</td>
<td>NS</td>
<td>Kim 2003</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td></td>
<td>Flatulence ↓</td>
<td>Kim 2005</td>
</tr>
<tr>
<td><em>L. rhamnosus</em> (± others)</td>
<td>24</td>
<td>6-24 weeks</td>
<td>NS</td>
<td>O’Sullivan 2000</td>
</tr>
<tr>
<td></td>
<td>103</td>
<td></td>
<td>Symptom score ↓</td>
<td>Kajander 2005</td>
</tr>
<tr>
<td></td>
<td>64</td>
<td></td>
<td>Distension ↓</td>
<td>Bausserman 2005</td>
</tr>
<tr>
<td><em>L. reuteri</em></td>
<td>54</td>
<td>24 weeks</td>
<td>NS</td>
<td>Niv 2005</td>
</tr>
<tr>
<td><em>B. infantis</em></td>
<td>75</td>
<td>4 weeks</td>
<td>↓ Pain, Bloating, BM difficulty</td>
<td>O’Mahony 2005</td>
</tr>
<tr>
<td></td>
<td>362</td>
<td></td>
<td></td>
<td>Whorwell 2006</td>
</tr>
</tbody>
</table>
Rifaximin

- RCT in 87 IBS patients recruited by media advertisement
- Rifaximin 400mg t.d.s. versus placebo X 10 days

• Caveats
  – Unvalidated outcome measure
  – Rationale uncertain
  – Adverse community effect of widespread use of antibiotics

Conclusions &
Take home messages

Every patient is an individual

Laurence S. Lowry 1887-1976
Conclusions

• IBS is multidimensional
• Significant somatization is found in about 50% of IBS patients →
  – Cognitive behavioural therapy / psychotherapy
  – Antidepressants
• 50% IBS lacking somatisation / anxiety / depression →
  – gut directed treatment
Selection of IBS patients for treatment
Vision of the future!

Predominant bowel symptom

Constipation
- Bulking agents
- 5HT₃ & 5HT₄ agonists
- Lubiprostone?
- Linaclotide?

Diarrhoea
- Diet
- Loperamide
- 5HT₃ antagonists

Diet
- Loperamide
- 5HT₃ antagonists

Bloating

Pain
- Antispasmodics
- Tricyclics

Psychometrics
- PHQ12

Cognitive behavioural therapy

Hypnosis

Prokinetics
- Probiotics?
- Antibiotics ?
- Tricyclics
Future Targets in IBS therapy?

- Mast cell activation
  - Mesalazine / Cromoglycate
- TRPV1 over expression
  - TRPV1 antagonists
- Fecal serine proteases
- CRF antagonists
Thank you for listening
Tailoring treatment to the multiple dimensions of IBS

Antidepressants
Cognitive behavioural therapy

Antispasmodics
Tricyclic anti-depressants
Anti-inflammatory?
Mast cell stabilisers?

Antimotility?

Visceral hypersensitivity

Somatisation

Constipation
Bulking agents (ispaghula, diet)
[Stimulants (pain)]
Secretagogues (lubiprostone, linaclotide)
Serotonergic agents- Tegaserod, Prucalopride

Diarrhoea
Loperamide
5HT3 antagonists
Diet
Loperamide for IBS symptoms: benefit for diarrhoea > pain / discomfort

- 21 D-IBS patients
- 11 placebo, 10 loperamide
  2-8mg nocte (dose titration allowed)
- 3 months treatment

Lavo et al. Scandinavian Journal of Gastroenterology 1987;22(Suppl. 130):77-80