Irritable Bowel: Complementary Therapy (ACT’s/CAM’s)
What is the Evidence

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HIPPOCRATES ‘THE FATHER OF MEDICINE’

- Hippocrates 5th century BC
- The ‘healing power’ of nature
- ‘Non-drug’ remedies:
  - blood letting
  - special diets
  - baths
  - exercise or rest
  - application of heat or cold
- Cited 300 medications most of which were of plant origin
FACULTY/PRESENTER DISCLOSURE

• **Faculty:** Dr. Connie Switzer

• **Relationships with commercial interests:**
  - Speakers Bureau/ Honoraria: Takaeda
  - Advisory Board/ Consulting Fees: Ferring; Takaeda
LEARNING OBJECTIVES

• At the end of this presentation, participants should understand:
  • That IBS is a very common problem
  • That IBS is a chronic and frustrating problem
  • That conventional therapies are not always of benefit
  • The evidence for use of CAM’s in IBS
IBS

- Affects 5-20% of individuals worldwide
- Annual incidence (US) 196-260 cases per 100,000
- F:M (2:1)
- Symptoms vary in severity from person to person and over time (mild to severe)
- Direct negative impact on QoL
- Minority seek medical advice (10-50%)
- Total annual costs (2000) Canada: $1.4 Billion
  - Direct costs (25%): $350 Million
  - Indirect costs (75%): $1 Billion
IBS: IMPACT ON QOL

- IBS ↓’s QoL to same degree as: DM, CHF, CRF, CLF
- Impact of IBS on QoL*
  - 86% change activities
  - 79% change diet
  - 61% interferes with interpersonal relationships
  - 43% mood changes
  - 43% dissatisfied with conventional health care

- 50% turn to complementary & alternative medicine

* Mertz et al 1995 Gastro, 109; 40-52
ROME III CRITERION FOR IBS

- Recurrent abdominal pain or discomfort at least 3 days per month in the past 3 months and at least 2 of the following
  - Improvement of pain with defecation
  - Onset associated with a change in frequency of stool. OR
  - Onset associated with a change in the form (appearance) of stool
ROME III: IBS

- Symptoms that cumulatively support the diagnosis are:
  - Abnormal stool frequency (>3 BM’s/day or <3 BM’s/wk)
  - Abnormal stool form
  - Abnormal stool passage (straining, urgency, incomplete evacuation)
  - Passage of mucous
  - Bloating or feeling of abdominal distension
SUBTYPES OF IBS

**IBS-C**: constipation predominant with hard or lumpy stools >25% and loose or watery stools <25% of BM’s

**IBS-D**: diarrhea predominant with loose or watery stools >25% and hard or lumpy stools <25% of BM’s

**Mixed IBS**: loose or watery stools >25% and hard or lumpy stools >25% of BM’s

Unclassified
IBS: EXTRA-INTESTINAL MANIFESTATIONS

- Gynaecologic
  - Dysmenorrhea, dyspareunia, pelvic pain syndrome
- Urologic
  - Dysuria, frequency
- Musculoskeletal
  - Fibromyalgia, chronic low back pain, headache
- Fatigue
- Psychological
  - Mood disorders, depression, anxiety
  - High incidence of abuse (sexual, physical)
  - Sleep disorders
"I thought it might help if I listed my symptoms."
DIAGNOSIS

- Probability of organic disease IBS = controls
- Pretest probability of IBD, CRC and infectious diarrhea is <1%
- Investigations should be case by case basis
- Screening for Celiac disease reasonable: 5% incidence in IBS (double controls)
- Patients over age 50 or with a FHx of IBD, CRC, polyps or other colon disease: colonoscopy
- Diarrhea predominant: R/O IBD and Celiac
  - Radiologic
  - Serologic markers: CRP, ASCA, pANCA
RED FLAGS

- Weight loss
- Anemia
- Arthritis, skin rash
- Fever
- Night-time symptoms
- FHx IBD and CRC
- Age $>$ 50 years
- Intractability, excessive pain
- Abnormal labs or exams
IBS: PATHOPHYSIOLOGY

- Altered Brain-GUT interactions
  - 5HT-mediated visceral sensitivity and gut motility

- Motility disturbance
- Visceral hypersensitivity

- Normal perception of abnormal motility, OR abnormal perception of normal motility
IBS: PATHOGENESIS

- Genetics: 1/3 have FHx of IBS
- Environment
- Dietary: 60% patients report food triggers
- Intestinal Flora
- Low grade inflammation: 25% IBS-D prior GI infection
- Abnormalities of NEC’s: alteration in 5Ht/Ghrelin
- Psychological
WHAT PATIENTS ‘KNOW’ ABOUT IBS

• Misconceptions
  • 52%: IBS caused by lack of enzymes
  • 43%: IBS is a form of colitis
  • 48%: IBS will worsen with age
  • 43%: IBS can develop into colitis
  • 38%: IBS can develop into malnutrition
  • 21%: IBS can develop into cancer

Halpert Am J Gastro; 2007: 102; 1972
WHAT PATIENTS WANT TO KNOW ABOUT IBS

- 68%: What foods to avoid
- 62%: Cause of IBS
- 59%: Coping strategies
- 55%: Medications
- 52%: Will they live with it for life

Halpert Am J Gastro; 2007: 102; 1972
## CONVENTIONAL IBS THERAPIES

<table>
<thead>
<tr>
<th>IBS-D</th>
<th>IBS-C</th>
<th>Pain/Bloating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorbants</td>
<td>Fiber supplements</td>
<td>Anxiolytics</td>
</tr>
<tr>
<td>GI relaxants</td>
<td>Osmotic laxatives</td>
<td>Anti-spasmodics</td>
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<tr>
<td>Anti-diarrheals</td>
<td>Probiotics</td>
<td>Anti-gas</td>
</tr>
<tr>
<td>GI Stimulants</td>
<td>SSRI’s</td>
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<td></td>
<td>TCA’s</td>
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</tbody>
</table>

Remember: 50% placebo response in all trials
ALTERNATIVE THERAPIES

- Diet
- Herbal and/or Enzymes
- Probiotics
- Mind-Body therapies
WHY DO PATIENTS USE ACT’S

- IBS:
  - Cure is rare; life-long condition
  - Cause of IBS is not well understood
  - Conventional therapy does not work in 25-40% pts
  - Conventional therapies make some patients worse
  - Placebo response in IBS is high (40-50%)
  - Home remedies have been used for centuries
  - Loss of trust in traditional therapy and providers
DIET AND IBS

- Fiber
- Low FODMAP diets
- Food allergy ‘elimination diets’ and food chemical restriction
- Gluten restriction
FIBER

- Soluble fiber may be of benefit in IBS
  - Psyllium (ground seed of plantago)
  - Forms a gel in H2O and is fermented by colonic bacteria
  - Metabolites ↓ Gut transit time & intra-colonic pressure
- 2 systematic reviews including:
  - Cochrane review of bulking agents
    - No effect on abdominal pain (RR 1.22, 95% CI 0.86-1.73)
    - No effect on global assessment (RR 1.09; CI 0.78-1.50)
    - No effect on symptom score (RR 0.93; CI 0.56-1.54)
  - Systematic review on soluble fiber (plantago)
    - Improved overall global IBS symptoms esp IBS-C
      - RR: 1.33 (95% CI 1.19-1.50)
    - Good evidence that SOLUBLE fiber improves constipation & global IBS symptoms

Shen and Nahas; CFP; 2009; 55: 143-148
• Consistently a LACK of evidence for food allergy in IBS
• No change in reliable immunologic markers with challenge or trigger foods
• “Food intolerances” – very difficult to study
  • Immediate or delayed
  • Severity highly variable and may or may not be dose dependant
  • May be identified only through food journals
• CHO malabsorption: may cause GI symptoms
FODMAP’S

- Fermentable Oligo, Di and Monosaccharides and Polyols
- Poorly absorbed and highly fermentable short-chain CHO’s
- Result in gas production
- Increased luminal fluid (osmotic effect)
- Abdominal distension and increased peristalsis
LOW-FODMAP DIET

• Evolving evidence for a role of poorly absorbed, short-chain CHO (lactose, fructose, sorbitol)
• Early data: lowFODMAP diet beneficial to some patients with IBS
• Retrospective chart audit (2005) low fructose
• RPCT – Rechallenge (Shepherd et al 2008)
  • All patients improved on low-FODMAP diet
  • Symptoms recurred with re-challenge
  • Placebo response minimal
• Diet control trial (Staudacher et al; 2011): FODMAP diet superior to standard dietary approach
LOW FODMAP DIET

- Highly restrictive
- Difficult to follow
- Careful nutritional assessment and follow up required
- Risks for micro-nutrient deficiencies
- Many challenges including eating out
FOOD ELIMINATION DIETS

• Very difficult to complete
• Very difficult to interpret

• Food Chemical intolerance
  • Very little science
  • Elimination for food chemicals includes: restriction of salicylates (found in fruits, vegetables, herbs, spices, nuts, tea, coffee), amines (chocolate, canned/smoked fish, sauces, stock, nuts, seeds, vinegar and some fruits and vegetables); MSG (soy sauce, strong cheeses); preservatives benzoates, propionate, sulphites, nitrites, sorbic acid; added antioxidants & food colors
  • No expert recommendation at this time
WHAT ABOUT GLUTEN IN IBS

• R/O Celiac disease BEFORE trying a gluten free diet
  • atTG and total IgA level
  • Duodenal biopsy if serology abnormal BEFORE GFD
  • 5% may have negative atTG so if IBS-D: biopsy

• Very little data:
• 34 IBS pts with well controlled IBS symptoms on GFD:
  • Challenged with gluten products vs placebo
    • 68% pts exacerbation of symptoms within 1 wk with gluten challenge cf to 40% on placebo
    • All improved with reinstitution of GFD

Biesiekierski et al; AJ G; 2011
SUMMARY OF ALTERNATIVE DIET RX

- Emerging evidence for the role of food intolerance in management of IBS symptoms
- NOT a cure but may improve symptoms and QoL
- Low FODMAP: improves symptoms in at least 74% of patients with IBS
- Impact of food additives/chemical is more difficult to determine – NO high level evidence
- Non-Celiac gluten intolerance: may have a role in IBS
  - Test for Celiac FIRST
- Caffeine and fats may play a role in IBS symptoms
# Summary of Evidence for CAM Rx in IBS

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peppermint Oil</td>
<td>2 meta-analysis of 5 &amp; 4 RCT</td>
</tr>
<tr>
<td>Probiotics</td>
<td>Meta-analysis of 23 RCTs</td>
</tr>
<tr>
<td>Soluble fibre</td>
<td>Meta-analysis of 9 RCT</td>
</tr>
<tr>
<td>TXTF</td>
<td>Meta-analysis of 12 prospective trials</td>
</tr>
<tr>
<td>Hypnotherapy</td>
<td>1 Cochrane; 3 other systematic reviews</td>
</tr>
<tr>
<td>CBT</td>
<td>5 RCTs (3 individual CBT and 2 group CBT)</td>
</tr>
</tbody>
</table>

Shen and Nahas; CFP; 2009; 55: 143-148
WHAT ABOUT HERBAL THERAPIES

• Remember:
  • today’s herbs may be tomorrow’s medications
• Herbals remedies may have potent pharmacological properties:
  • Anti-spasmodics
  • Anti-emetic
  • Anti-pyretic
  • Anti-inflammatory
  • Colonic stimulants
  • ?Central effects: pain modulators
PEPPERMINT OIL

- Extract of peppermint plant (Mentha piperita)
  - Used for thousands of years to treat stomach ailments
- Relaxes intestinal smooth muscle cells by interfering with calcium channels
- Short term trials: 3-6 enteric coated caps/day
- 2 meta-analysis
  - Overall IBS symptom improvement **OR 2.7** (95%CI 1.6-4.8)
  - Symptom **improvement in up to 75%** of IBS pts cf to 38% on placebo
  - Alleviates: abdominal pain and other IBS symptoms

Shen and Nahas; CFP; 2009; 55: 143-148
OTHER SINGLE HERBALVS – NO BENEFIT IN IBS

- Aloe vera: PCDB (1 month)
- Curcuma Xanthorrhiza: DBRPC T (18 wks)
- Hypericum perforatum (St John’s Wort): RDBPCT: 12 wks
- Many open label trials on multitude of herbal remedies
- Methodology flaws significant
- Low numbers of patients; varied patient selection
- Poorly defined end points

Rahimi & Abdollahi; WJ G; 2012; 18(7): 589-600
<table>
<thead>
<tr>
<th>Herb Rx (#herbs)</th>
<th>Type Trial</th>
<th>Dur/type</th>
<th>BM’s better</th>
<th>Improved Pain/TSS</th>
<th>Improved QoL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carmint (3)</td>
<td>DBR PCT</td>
<td>8wk IBS</td>
<td>?</td>
<td>?/I</td>
<td>?</td>
</tr>
<tr>
<td>CHM (17)</td>
<td>RDB PCT</td>
<td>16wk IBS</td>
<td>I</td>
<td>?/I</td>
<td>I</td>
</tr>
<tr>
<td>C-IBS (4)</td>
<td>Open</td>
<td>2wk IBSC</td>
<td>I</td>
<td>I/?</td>
<td>?</td>
</tr>
<tr>
<td>DA-IBS (3)</td>
<td>Open</td>
<td>2wk</td>
<td>I</td>
<td>?/I</td>
<td>?</td>
</tr>
<tr>
<td>Iberogast (9)</td>
<td>DBR PCT</td>
<td>4wl OBS</td>
<td>?</td>
<td>I/I</td>
<td>I</td>
</tr>
<tr>
<td>Padma-lax (10)</td>
<td>RDB PCT</td>
<td>3mo IBSC</td>
<td>I</td>
<td>I/?</td>
<td>?</td>
</tr>
<tr>
<td>TXNG (4)</td>
<td>RDB PCT</td>
<td>3wk IBSD</td>
<td>I</td>
<td>I/?</td>
<td>?</td>
</tr>
</tbody>
</table>

Herbal combinations with NO therapeutic benefit IBS:
- TXYF (4): RPC T for IBSD (2wks)
- TCM (11): RPC T for IBSD (16wks)

Rahimi & Abdollahi; WJ G; 2012; 18(7): 589-600
MODIFIED IBEROGAST

- Modified Iberogast (chamomile flower, peppermint leaves, caraway fruit, licorice root, celandine herbs, milk thistle fruit) vs: Bitter Candy Tuft (BCT) vs placebo
- 157 pts, Randomized 7 days free of medications
  - 20 drops 3 times daily for 4 weeks
- Outcomes at 2 and 4 wks
  - Improved abdominal pain score
  - Improved global symptom score (GSS or TSS)

Madisch et al AGA: 2001 Abstract 715
SUMMARY OF HERBAL REMEDIES IN IBS

- Single preparations:
  - Best evidence for efficacy: Peppermint Oil
  - No or minimal benefit: Aloe vera, St John’s wort

- Multi-Compound preparations:
  - STW5 (Iberogast): hopeful (anti-inflammatory, prosecretory activity, GI motility effects)

- Traditional Iranian medicine: perhaps of benefit – quality of data low

Rahimi & Abdollahi; WJ G; 2012; 18(7): 589-600
PROBIOTICS

• Live organisms that when ingested in adequate amounts, exert a health benefit on the host

• Mechanisms of action:
  • Alter intraluminal milieu: produce SCFA
  • Luminal and anti-microbial effects (↓ harmful bacteria)
  • Potent anti-inflammatory activity, immune function
  • Effects on intestinal barrier function
  • Neuro-modulatory effects

• **Meta-analysis of 23 trials** (1404 pts)
  • Improvement in global IBS symptoms (RR 0.77, CI 0.62-0.94)
  • Improved abdominal pain RR 0.78; CI 0.69-0.88
  • Most beneficial strains: lactobacillus or bifidobacterium
  • Daily doses of 10-100 billion bacteria

Shen and Nahas; CFP; 2009; 55: 143-148
SLIGHT OVERALL BENEFIT FOR PROBIOTICS IN IBS CF TO PLACEBO

McFarland & Dublin; WJG; 2008; 14(7): 2650-2661
### Clinical trials of probiotics in IBS

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Duration</th>
<th>Probiotic</th>
<th>Clinical Score</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maupas</td>
<td>34</td>
<td>1 month</td>
<td><em>S. boulardii</em></td>
<td>Improved stool volume and consistency</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Halperin</td>
<td>18</td>
<td>4 months</td>
<td><em>L. acidophilus</em></td>
<td>Improved symptoms</td>
<td>p=0.01</td>
</tr>
<tr>
<td>Hunter</td>
<td>40</td>
<td>1 month</td>
<td><em>L. plantarum 299v</em></td>
<td>Improved global symptoms</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Nobaek</td>
<td>60</td>
<td>1 month</td>
<td><em>L. plantarum 299v</em></td>
<td>Improved global symptoms</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Niedzielin</td>
<td>40</td>
<td>1 month</td>
<td><em>L. plantarum 299v</em></td>
<td>Improved global symptoms</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Kim</td>
<td>25</td>
<td>2 months</td>
<td>VSL#3</td>
<td>Reduced bloating</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>O’Mahony</td>
<td>77</td>
<td>2 months</td>
<td><em>B. infantis</em></td>
<td><em>B. infantis</em> improved global symptoms and anti-inflammatory cytokine profile</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td></td>
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<td></td>
<td><em>Versus</em></td>
<td><em>L. salivarius</em> showed no benefit</td>
<td></td>
</tr>
</tbody>
</table>

N = number of patients  
*S. = Saccharomyces, L. = lactobacillus, B. = bifidobacterium*

TAKE HOME MESSAGE ON PROBIOTICS IN IBS

- Trials with positive benefit tend to be short trials
- Overall, probiotics use was associated with
  - **less likelihood of global IBS symptoms** cf to placebo
    - RR=0.77; 95% CI 0.62-0.94)
  - **Less likelihood of abdominal pain** at the end of F/U
    - RR=0.78; 95% CI 0.69-0.88)
  - There was NOT sufficient data to examine other individual IBS symptoms or efficacy of individual products/strains
- Adverse events: lack of reporting in most studies
  - ↑’d abdo symptoms, epistaxis, aftertaste, anxiety, angina
  - 15% of trials: NO report of safety data

McFarland & Dublin; WJ G; 2008; 14(7): 2650-2661
PREBIOTICS

- Nondigestable fermentable food components that result in stimulation of the GUT microbiota that confer health benefit to the host

- 4 RCT’s
- Fructan
  - Inulin, oligofructose
- Galacto-oligosaccharides
- ?variable effect IBS
MIND BODY THERAPIES

- Brain-GUT interactions:
  - Contribute to the pathogenesis of IBS
  - ~50% IBS patients comorbid psychiatric disorders

- Hypnotherapy
  - Cochrane review (4 trials):
    - Reduced IBS symptom scores (median change in score of 13/100 points cf to 4.5 points in control group p=0.008)
    - Safe, longer term benefits?

- Cognitive Behavioral Therapy (CBT)
  - 5 controlled trials - mixed results

- Acupuncture
  - 5 controlled trials in IBS; 2 systematic reviews
  - Insufficient evidence

Shen and Nahas; CFP; 2009; 55: 143-148
SUMMARY OF CAM’S IN IBS

- **Dietary therapy**
  - Soluble fiber may be of benefit for IBS-C
  - LowFODMAP diet may be of benefit for gas and bloating
  - Food Elimination/Food Allergy/Food chemical avoidance?
  - Gluten restriction MAY be of benefit: TEST FOR CELIAC FIRST

- **Herbal Therapies**
  - Therapies with peppermint oil, TXYF, Padma lax, psyllium, and Iberogast have evidence for efficacy

- **Probiotics**
  - Variable results but benefits for:
    - Lactobacillus plantarum, bifidobacterium longum, S.boulardi, VSL-3
  - Mind-Body therapies: may be of benefit in some patients
LEARNING OBJECTIVES

- Participants now understand:
  - That IBS is a very common problem
  - That IBS is a chronic and frustrating problem
  - That conventional therapies are not always of benefit
  - The evidence for use of CAM’s in IBS