

## Probiotics and Alternative Approaches to Managing Irritable Bowel Syndrome



- Anthony J. Lembo, M.D.
- Associate Professor of Medicine
- Beth Israel Deaconess Medical Center
- Harvard Medical School
- Boston, MA USA



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Life Style including exercise and diet

Probiotics

Acupuncture

Psychological Therapies

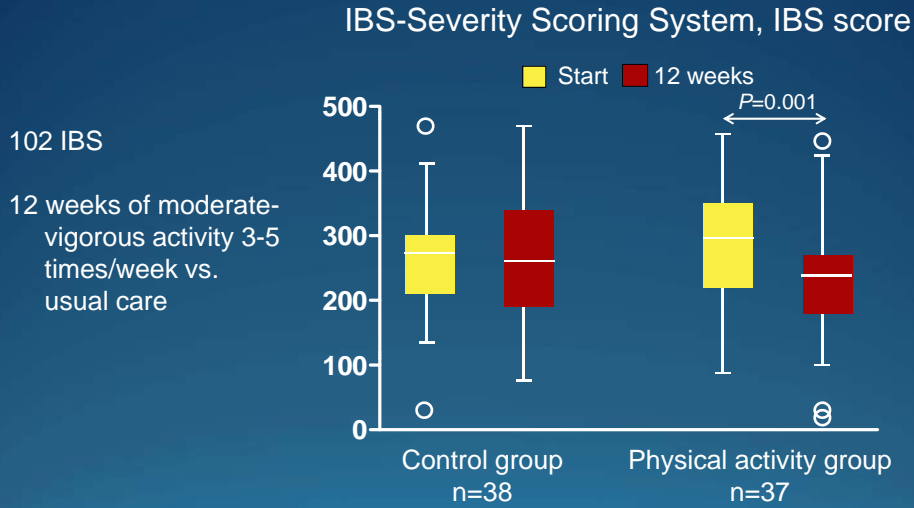
Herbs including peppermint oil



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## Impact of Physical Activity on IBS



Johannesson E, et al. Am J Gastroenterol, May;106(5):915-22

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## Fermentable oligo-, di-, monosaccharides and polyols (FODMAPs)



Excess Fructose

Honey, apples, pears, peaches, mangos, fruit juice, dried fruit



Fructans

Wheat (large amounts), rye (large amounts), onions, leeks, zucchini



Sorbitol

Apricots, peaches, artificial sweeteners, artificially sweetened gums



Raffinose

Lentils, cabbage, brussels sprouts, asparagus, green beans, legumes



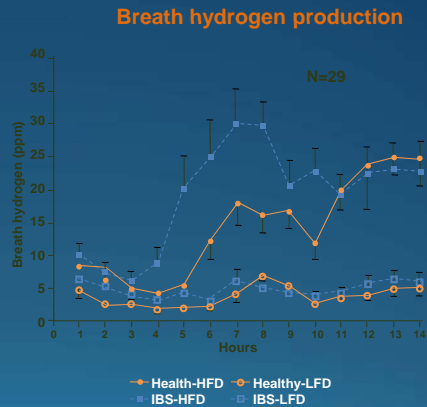
1. Shepherd SJ, et al. Clin Gastroenterol Hepatol. 2008;6:765-771;  
2. Shepherd SJ, Gibson PR. J Am Diet Assoc. 2006;106:1631-1639.

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## High FODMAP Diets Induce Increased Breath Hydrogen and Symptoms in IBS Patients

- Single-blind crossover
- 15 healthy/ 15 IBS
- 2-days
  - high-FODMAP diet (50 g/d)
  - low-FODMAP diet (9 g/d)
- GI sx's and lethargy induced by high FODMAP diet in IBS but not control patients



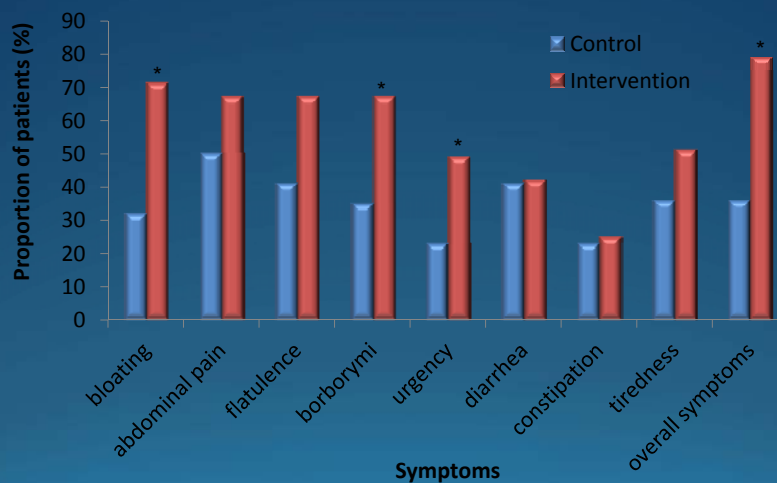
HFD=high-FODMAP diet; LFD=low-FODMAP diet

Ong DK et al. *J Gastroenterol Hepatol.* 2010;25:1366-1373.

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## Low-FODMAP Improves IBS Symptoms Compared to Control Diet



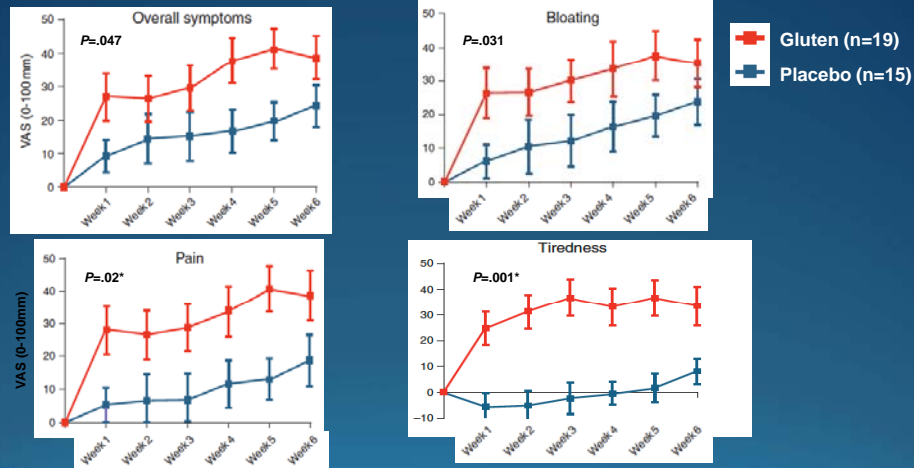
Staudacher HM, et al. *J Nutr* 2012;142:1510.

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# Gluten in IBS without Celiac Disease

## Mean Change in Symptoms Over 6 Weeks



\*P-value for analyses at Week 1 and entire study period. Biesiekierski JR, et al. *Am J Gastroenterol.* 2011



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# PROBIOTICS

- Live, viable microorganisms that, when administered in adequate amounts, confer a health benefit on the host
- May be found in foods, supplements, or drugs
- Available as single-organism or combination products

### Common Probiotics<sup>1-3</sup>

- Bifidobacterium*
- B infantis* 35624
- B animalis* DN-173010
- Lactobacillus*
- L salivarius* UCC4331
- L reuteri*
- L casei*
- L plantarum* 299v
- L rhamnosus* GG
- Saccharomyces boulardii*
- E coli* Nissle 1917

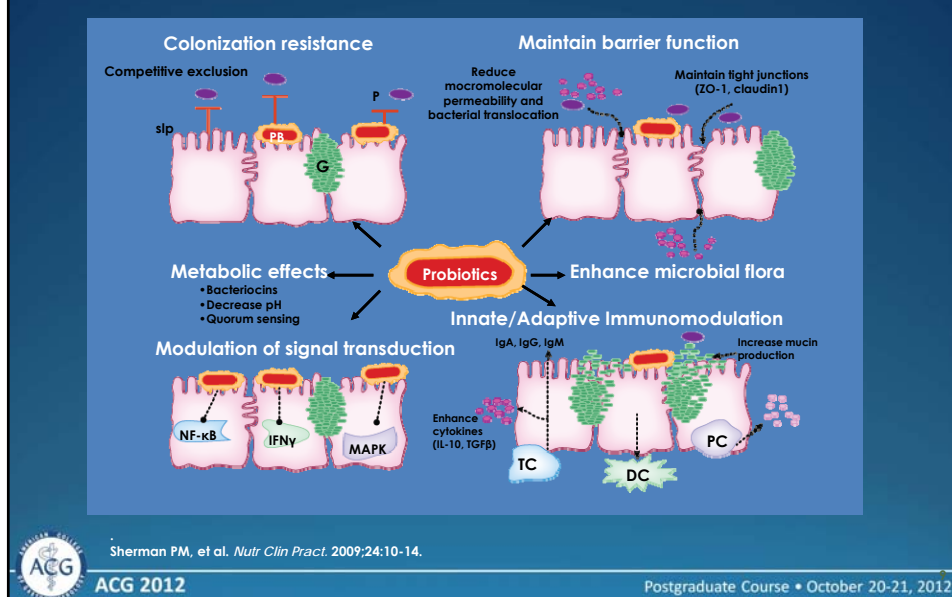
1. Douglas LC, Sanders ME. *J Am Diet Assoc.* 2008;108:510-521.  
 2. Quigley EMM, Rourke B. *Neurogastroenterol Motil.* 2007;19:166-172.  
 3. Shanahan F. *Am J Physiol Gastrointest Liver Physiol.* 2005;288:417-421.



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## Proposed Mechanisms of Probiotics



## Probiotics for IBS: Clinical Considerations

- Health benefits are strain-specific and dose-specific
  - Each strain and dose must be tested to assess efficacy
- Probiotics in US are foods or dietary supplements
  - Not regulated as drugs
  - Claims regarding disease benefits not allowed on product label

1. Food and Agriculture Organization of the United Nations and World Health Organization. 2002. [http://www.who.int/foodsafety/fs\\_management/en/probiotic\\_guidelines.pdf](http://www.who.int/foodsafety/fs_management/en/probiotic_guidelines.pdf).
2. Douglas LC, Sanders ME. *J Am Diet Assoc.* 2008;108:510-521.
3. Sanders ME. *Funct Food Rev.* 2009;1:3-12.



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## Meta-analysis Probiotics in IBS

- 10 RCTs involving 918 patients with dichotomous outcomes
- Probiotics were statistically significantly better than placebo
  - NNT=4 (95% CI 3 to 12.5).
  - Significant heterogeneity ( $\chi^2=28.3$ ,  $p=0.001$ ,  $I^2=68\%$ )
- **Conclusion:** “Probiotics appear to be efficacious in IBS, but the magnitude of benefit and the most effective species and strain are uncertain”



Moayyedi P et al. Gut 2010;59:325-332

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## Efficacy of Probiotics in IBS: Dichotomous Data

	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
<b>Lactobacillus (3 studies)</b>					
Subtotal (95% CI)	36 / 70	55 / 70	26.88	0.64	(0.41, 1.02)
<b>Combination (4 studies)</b>					
Subtotal (95% CI)	69 / 151	103 / 151	37.23	0.66	(0.36, 1.20)
<b>Bifidobacterium (2 studies)</b>					
Subtotal (95% CI)	156 / 300	75 / 122	23.66	0.80	(0.56, 1.13)
<b>Streptococcus (1 study)</b>					
Subtotal (95% CI)	20 / 32	19 / 22	12.23	0.72	(0.53, 0.99)
<b>Total</b>					
(95% CI)	281 / 553	252 / 365	100.00	0.71	(0.57, 0.88)



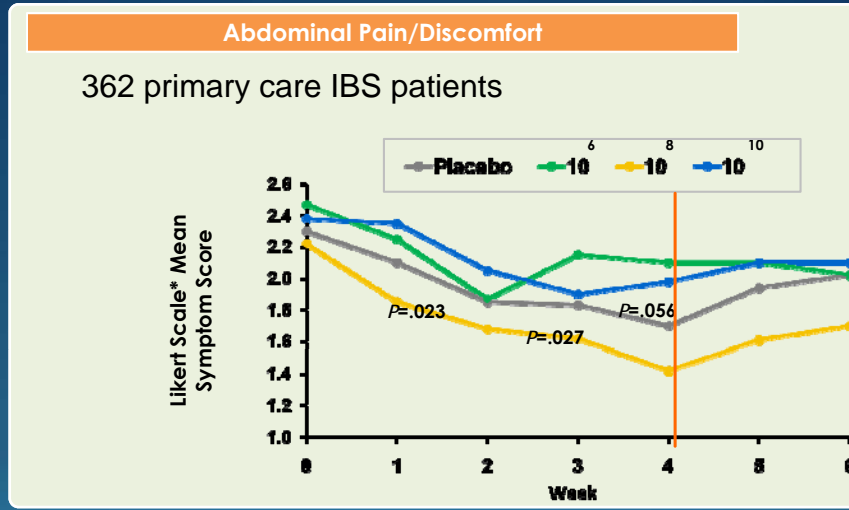
Moayyedi P et al. Gut. 2010;59:325-332.

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Favors treatment - Favors control

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## Bifidobacterium infantis 35624 for IBS



\*Likert scale=0 (none) to 5 (severe); treatment was stopped at 4 wks.

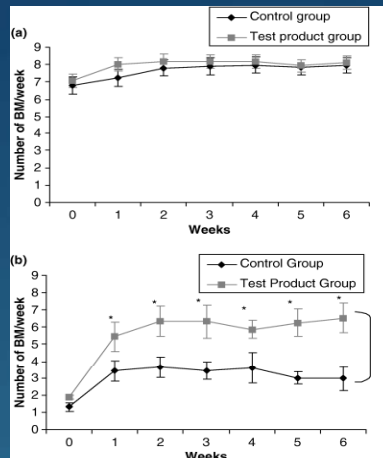
Whorwell PJ, et al. *Am J Gastroenterol.* 2006;101:1581-1590.



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## Bifidobacterium animalis DN 173 010 (B. regularis) for IBS



Intention-to-treat population  
N= 267

Patients with < 3 BM/wk  
N=19

Guyonnet et al. *Aliment Pharmacol Ther* 2007;26:475

Fermented milk product (Activia)  
B. animalis 1.25 x 10<sup>10</sup> CFU per serving  
S. thermophilus & L. bulgaricus



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## Multispecies Probiotic Mixture in IBS-D

7 species of probiotic bacteria:

Lactobacilli acidophilus, plantarum, rhamnosus

Bifidobacteri breve, lactis, longum

Streptococcus thermophilus

One capsule B.I.D. x 8 wks ( $1.0 \times 10^{10}$  cells/d)

n=50

Adequate Relief 50% of weeks

48% probiotic vs. 12% placebo,  $P=0.01$

Stool consistency: probiotics > placebo  $P<0.05$

No effect on individual symptom scores

Ki Cha et al., J Clin Gastro 2012 Mar;46(3):220-7

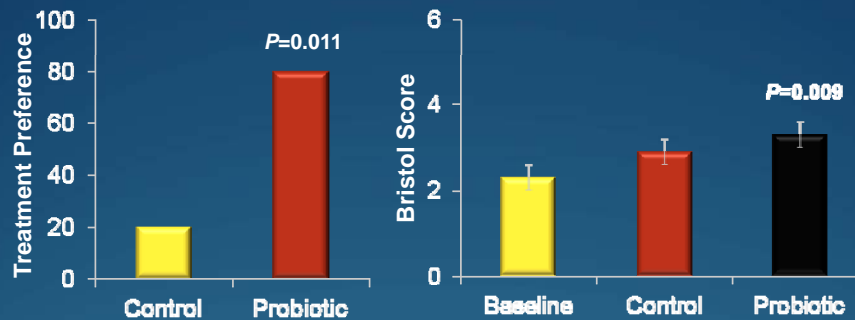


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## Lactobacillus paracasei enriched artichokes for Chronic Constipation

A double-blind, randomized, crossover trial



- 20 CC pts randomized to 180 g ordinary artichokes vs. artichokes with *L. paracasei* ( $2 \times 10^{10}$  CFU) x 15 days
- Improvements also reported for frequency, hard stools, and feeling of incomplete evacuation



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Riezzo G, et al. Aliment Pharmacol Ther 2012;35:441

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## Probiotics for IBS: Summary

- Most studies are small, single-center
- Current evidence suggests that probiotics may be effective
- Best evidence to date is with *B. infantis*
- Further studies are clearly needed to assess dose, duration of the therapy and the appropriate patient



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## Complementary and Alternative Medicine (CAM) use is common in the USA

- Medical treatments not commonly considered to be a part of conventional medicine
- Between 1997-2002 ~ 35% of the population used CAM<sup>1</sup>
- In an HMO clinic use of CAM was reported by ~ 35% of patients with FBD with an annual cost of \$200<sup>2</sup>
  - Women, higher education, anxiety



Tindle HA, et al.. *Altern Ther Health Med* 2005;11:42-9  
van Tilburg MA, *BMC Complement Altern Med* 2008;8:46.

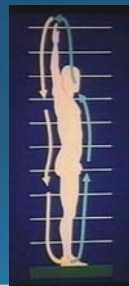
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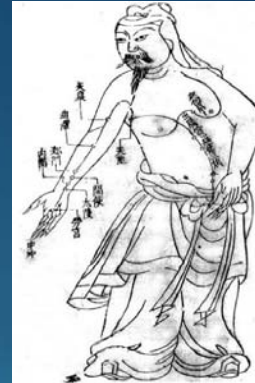
## Acupuncture: Basic Principles

- Targets the state of 'disharmony', imbalance in the yin-yang and its connecting qi.

Yang



Yin

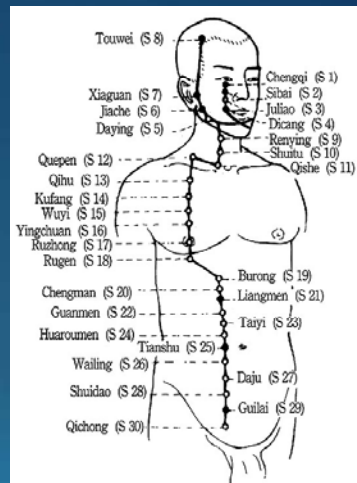


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## Acupuncture: Basic Principles

- 365 traditional acupuncture points on 14 main channels (meridians)
- Each point has defined therapeutic actions
- 5-15 needles are used in a session; combinations varying during a course of sessions

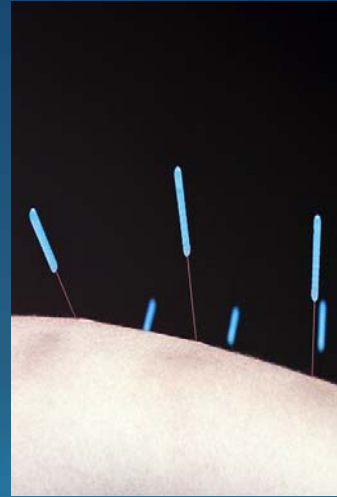


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## Acupuncture: Basic Principles

- After puncturing the skin needles are moved back & forth
- Needles are left in place for 15-20 minutes



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## Basic Theory: Acupuncture

- Other therapies commonly used during acupuncture treatment:
  - Massage
  - Cupping
  - Heat
  - Electrical stimulation
  - Scarification (counter irritation)
  - Lifestyle counseling



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## NIH Consensus Panel Recommendations for Acupuncture

- Efficacious for:
  - adult post-op and chemo induced nausea and vomiting and probably for nausea of pregnancy
  - Post-op dental pain
- Quality or quantity of research evidence for other diseases are not sufficient to provide firm evidence



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## Specific Challenges in Performing Acupuncture Trials

- Inherent bias by the acupuncturist
- Matching sham control
  - Penetrating, non-penetrating, location
- Heterogeneity of acupuncture techniques
- Individuality of treatment according to 'patterns of disease' is difficult to incorporate into a RCT
- Non-specific effects



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## Acupuncture for IBS: Systematic Review and Meta-Analysis

- 17 RCTs (N=1,806)
- Heterogeneity: interventions, controls, and outcomes
- Sham-controlled RCTs have found no benefits of acupuncture relative to a credible sham acupuncture control on IBS symptom severity or IBS-related QOL.

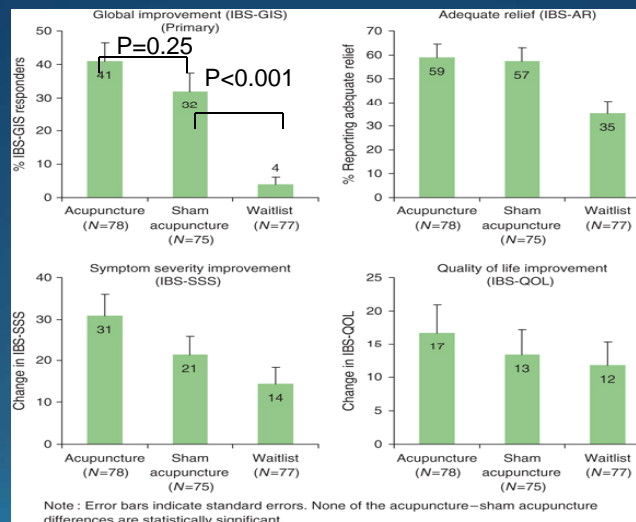


Manheimer E, et al. *Am J Gastroenterol* 2012; 107:835–847

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## Acupuncture IBS Clinical Trial



Lembo A, *Am J Gastroenterol* 2009; 104:1489 – 1497;



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## Acupuncture in IBS: Summary

- Acupuncture/sham acupuncture are superior to Waitlist Control
  - Is sham acupuncture active therapy?
  - Non-specific (i.e., placebo) effects?
- Recent trials have shown acupuncture to have a small non-significant effect on IBS symptoms
  - ? If other therapies were added to acupuncture (e.g., cupping, electrical activation)
  - ? Subset of IBS
  - ? A larger trial (e.g., n=970) would be needed to adequately power a larger more definitive study



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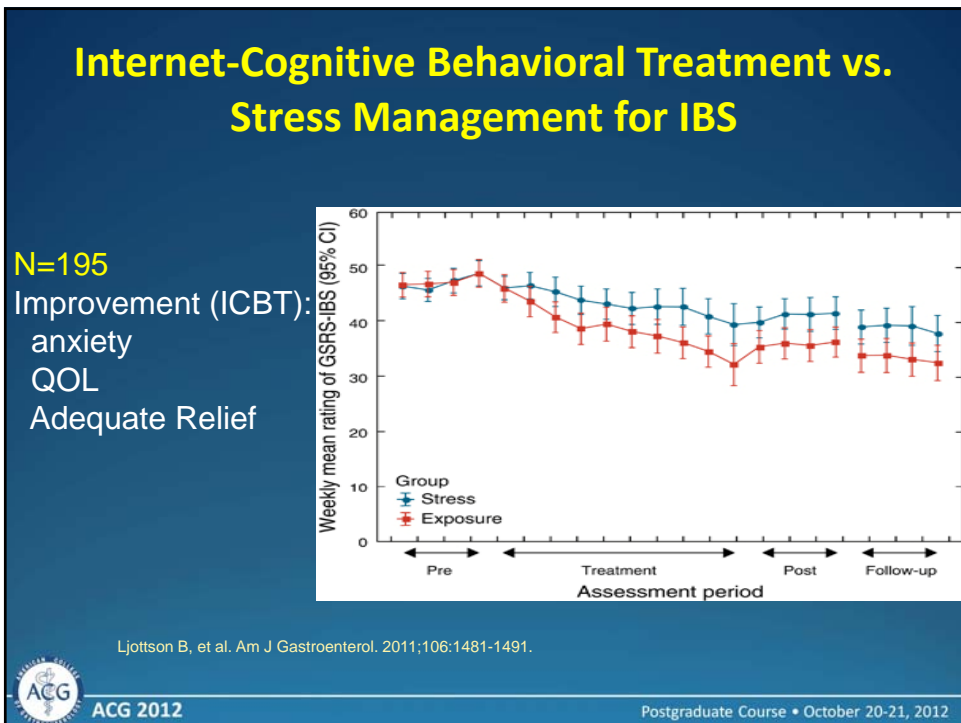
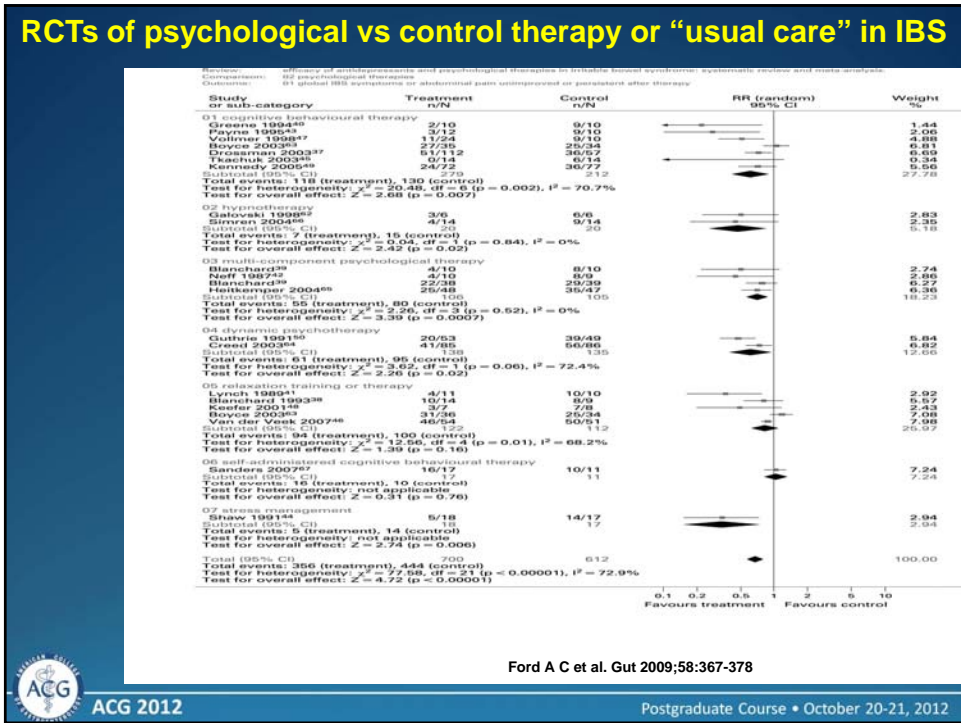
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## Psychological Therapies for IBS



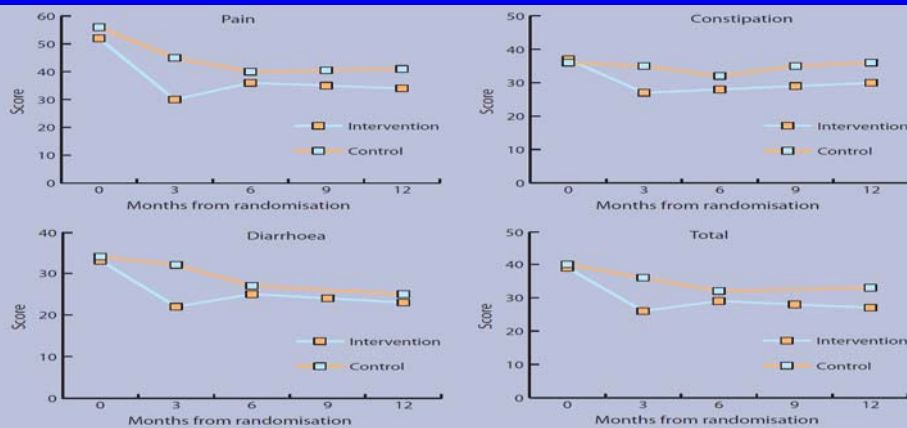
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## Hypnosis in IBS

24 general practices in the UK  
86 pts – failed initial therapy  
5 30 min sessions of gut-directed hypnotherapy vs. usual care



Roberts et al. Br J Gen Pract. 2006 February 1; 56(523): 115

## Hypnotherapy for IBS

- 4 studies (n=147) met inclusion criteria
  - 1 study (Whorwell, 1984): hypnotherapy vs. psychotherapy and placebo pill
  - 2 studies (Paulson, 2002; Galvoski, 1998) hypnotherapy vs. waiting-list controls
  - 1 study (Roberts, 2006) hypnotherapy vs. usual medical management.
- Hypnotherapy > waiting list control or usual medical management
  - abdominal pain, composite primary IBS symptoms
- AEs not reported in any of the trials.
- Quality was inadequate to allow any conclusion about the efficacy of hypnotherapy for IBS



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Webb AN [Cochrane Database Syst Rev](#). 2007 Oct 17;(4):CD005110.

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## Herbal Therapies for IBS



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## Peppermint Oil in IBS



- Obtained by steam distillation of the aerial parts of the flowering plant *Mentha piperita*
- Active ingredient: menthol (calcium channel blocking activity)
- Meta-analysis (1998)
  - 8 trials. 5 trials were DBPC.
  - Significant ( $P < .001$ ) global improvement of IBS
- A Subsequent RDBPC in Taiwan (n=110 IBS pts) x 4 weeks
  - Peppermint - < abd distention, stool frequency, and flatulence. 79% of the patients also had alleviation of abdominal pain.



Pittler MH. Peppermint oil for IBS. *Am J Gastroenterol* 1998;93:1131-5.  
Liu JP. Enteric-coated peppermint-oil capsules in IBS. *J Gastroenterol* 1997 Dec;32(6):765-8.

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## Peppermint Oil Improves Abdominal pain/ discomfort

90 IBS patients in Iran were randomized to enteric-coated, delayed-release peppermint oil (Colpermin) or placebo tid.

	Week 0	Week 1	Week 4	Week 8
<b>None</b>				
Placebo	0 (0%)	9 (33%)	11 (41%)	6 (22%)
Colpermin	0 (0%)	6 (18%)	14 (42%)	14 (42%)
<b>Occasional</b>				
Placebo	17 (63%)	15 (56%)	10 (37%)	7 (26%)
Colpermin	15 (46%)	18 (55%)	11 (33%)	14 (42%)
<b>Persistent</b>				
Placebo	9 (33%)	3 (11%)	6 (22%)	14 (52%)
Colpermin	14 (42%)	8 (24%)	7 (21%)	5 (15%)

Merat et al. Dig Dis Sci. 2010 May;55(5):1385-90



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## Meta-analysis of Herbs in IBS



- Only 4 studies good quality
- “Herbal medicines should be used with caution. It is necessary to conduct rigorous, well-designed clinical trials to evaluate their effectiveness and safety in the treatment of IBS”

Shi J, et al. World J Gastroenterol 2008;14:454–62.



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## Herbs in IBS: TXYF

- Tong xie yao fang (TXYF)
  - rhizoma atractylodis macrocephalae, radix paeoniae alba, pericarpium citri reticulatae, and radix saposhnikoviae.
- Meta-analysis 12 studies (2006)
  - TXYF > conventional therapies
- Subsequently (2009)
  - TXYF (n=80) vs. Miyarisan, a probiotic (butyric acid bacteria), (n=40) for 4 weeks
  - no significant difference
  - # activated mast cells decreased in the TXYF group



\$10.95

Bian et al. . J Altern Complement Med 2006;12:401–7.  
Pan, et al. Chin J Integr Med 2009;15: 216–9.

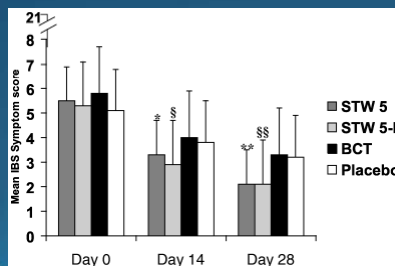


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## Herbs in IBS: STW 5

- bitter candytuft, chamomile flower, peppermint leaves, caraway fruit, licorice root, lemon balm leaves, celandine herbs, angelica root, milk thistle fruit.
  - STW 5-II: does not include angelica root and milk thistle fruit.
- Mutli-center RDBPC with 208 IBS pts
  - STW 5, STW 5-II, bitter candytuft monoextract (BCT), or placebo for 4 weeks.



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Madisch Aet al. ACP Postgraduate Course • October 20-21, 2012

## Herbs in IBS: Padma Lax



- Tibetan herbal formula:
  - dry extract of Aloe, calumba root, cascara, chebulic myrobalan fruit, condurango, elecampane, frangula bark, gentian root, ginger, heavy kaolin, long pepper, nux vomica, rhubarb, sodium hydrogen carbonate, and sodium sulfate.
- RDBPC IBS-C
  - Padma Lax significantly improved constipation, abdominal pain, incomplete evacuation, abdominal distension, and flatus/flatulence
  - AEs loose stools in a small number of subjects, but they responded well after lowering the dosage.

"Pure Relief in a Bottle"



Sallon S et al. *Digestion* 2002;65:161–71.



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## Summary

- Lifestyle modifications, particularly exercise and dietary modification, may improve symptoms of IBS
- CAM therapies may have a role in treating some patients with IBS
- High quality multi-center placebo controlled trials are needed to further define this role
- Side effects, particularly with herbs, need to be well characterized



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