Probiotics, Special Diets, and Complementary Therapies: We Know Patients Want Them, So What Do We Tell Them?

Sandra C. Kim, MD

December 5, 2014

Advances in IBD 2014

Nationwide Children's
When your child needs a hospital, everything matters.℠

The Ohio State University

Disclosures

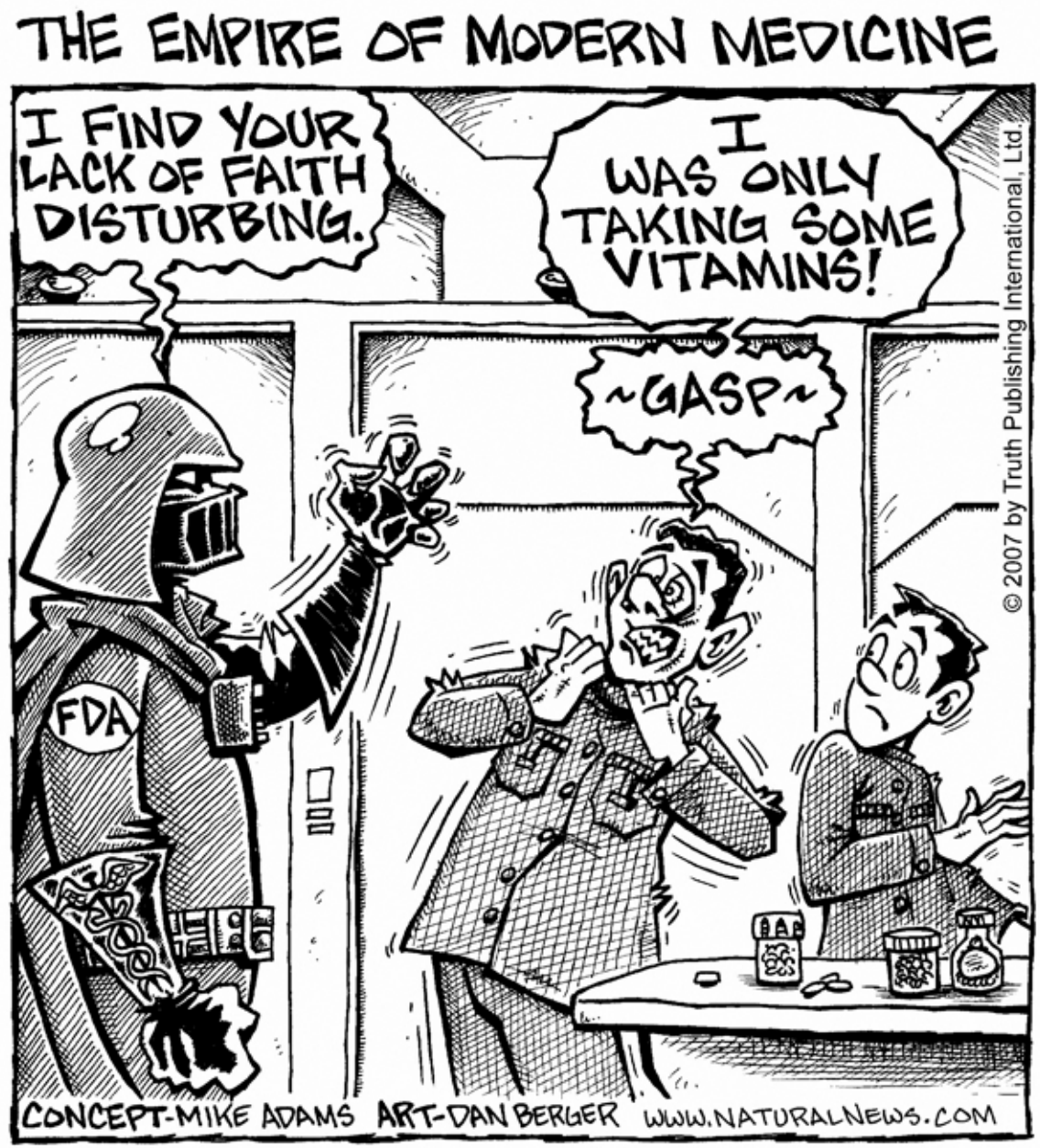
I have the following disclosures:

Speaker: Nestle Nutrition and Abbott Laboratories
Consultant: AbbVie Pharmaceuticals

Objectives

- How do we define complementary/integrative medicine?
- Patients' perceptions of CAM
- Efficacy of therapies in IBD
  - Herbal agents
  - Medications
  - Nutrition/Diet
  - Mind – body practices
- What should the pediatric GI team do?

The Patient's View of How We View CAM?



What DO We Think About CAM?

Defining CAM and Integrative Medicine

- CAM constitutes “a group of diverse medical and healthcare systems, practices, and products that are not presently considered part of conventional medicine”
- Different categories
  - Mind-Body
  - Manipulative and Body-Based Practices
  - Energy Medicine
  - Biologically-Based Practices

What is Integrative Health Care?

- Emphasizes healing of the whole person to achieve health goals
  - Physical
  - Emotional
  - Mental
  - Spiritual
  - Social
- Fosters healthy habits in a healthy habitat via lifestyle strategies, conventional, and complementary care

National Trends in CAM Use

- 2007 NHIS survey by the CDC
  - 42% adults and12% children used within 12 mos
- $33.9 billion spent on CAM modalities
- Most common in those with chronic conditions; females; educated; affluent; health-conscious
- Most commonly used:
  - Diets and dietary supplements
  - Mind/body (deep breathing, meditation, yoga)
  - Chiropractic

Barnes, *et al* (2007). *Natl Hlth Stat Rep*
Nahin, *et al* (2008). *Natl Hlth Stat Rep*

CAM Usage in Pediatric IBD Patients

- CAM used by 40-56% in pediatric IBD patients
- The most commonly used CAM therapies in the IBD group: megavitamins, dietary supplement, spiritual interventions, and herbal medicine
- Positive predictors for CAM include self-reported overall health, poor quality of life, increase side effects with allopathic medications, ethnicity, and and parental education.
- Majority interested in learning about CAM

Heuschkel, *et al* (2002). *AJG*
Markowitz, *et al* (2004). *Inflamm Bowel Dis*
Wong, *et al* (2009). *JPGN*
Serpico, et al (2014). *Inflamm Bowel Dis* (abstract)

Manitoba IBD Cohort Study

Table 2 Percentage of complementary and alternative medicine (CAM) usage across time for the total sample, disease subtypes, and gender

	Month 0	Month 12	Month 30	Month 54
Total sample use n=309				
CAM services only	21	25	18	25
CAM products only	11	10	11	9
Both CAM services and products	10	14	11	13
Any CAM service/product	42	49	43	49
Disease subtypes and any CAM use				
Crohn's disease (n=156)	19	25	23	26
Ulcerative colitis (n=153)	23	25	20	23
Gender and any CAM use				
Men (n=116)	15	15	11	15
Women (n=193)	27	34	32	34

- 74% overall used CAM; ~40% at given time point
- Only 18% for IBD primarily

Rawsthorne, *et al* (2012). *Gut*

Efficacy of Herbal Therapies in Crohn's

Author, reference	Country	Year	CAM	Number	Comparator	Duration	Remission on CAM (%)	Remission on comparator (%)
Omer[36]	USA	2007	Artemisia absinthium	40	Placebo	10 weeks	65%	0%
Krebs[37]	Germany	2010	Artemisia absinthium	20	Placebo	6 weeks	80%	20%
Gerhardt[38] (article in German)	Germany	2001	Boswellia serrata extract H15	102	Mesalazine	8 weeks	36%	31%
Ren[42]	China	2007	Tripterygium wilfordii	20	Placebo	12 weeks	–	–
Holtmeier[39]	Germany	2010	Boswellia serrata extract (Boswelan, PS0201Bo)	108	Placebo	52 weeks	60%	55%
Tao[40] (article in Chinese)	China	2009	Tripterygium wilfordii (post-op CD)	45	Mesalazine	6 months 12 months	82% (6 months) 68% (12 months)	78% (6 months) 61% (12 months)
Liao[41] (article in Chinese)	China	2009	Tripterygium wilfordii (post-op CD)	39	Sulphasalazine	–	94%	75%

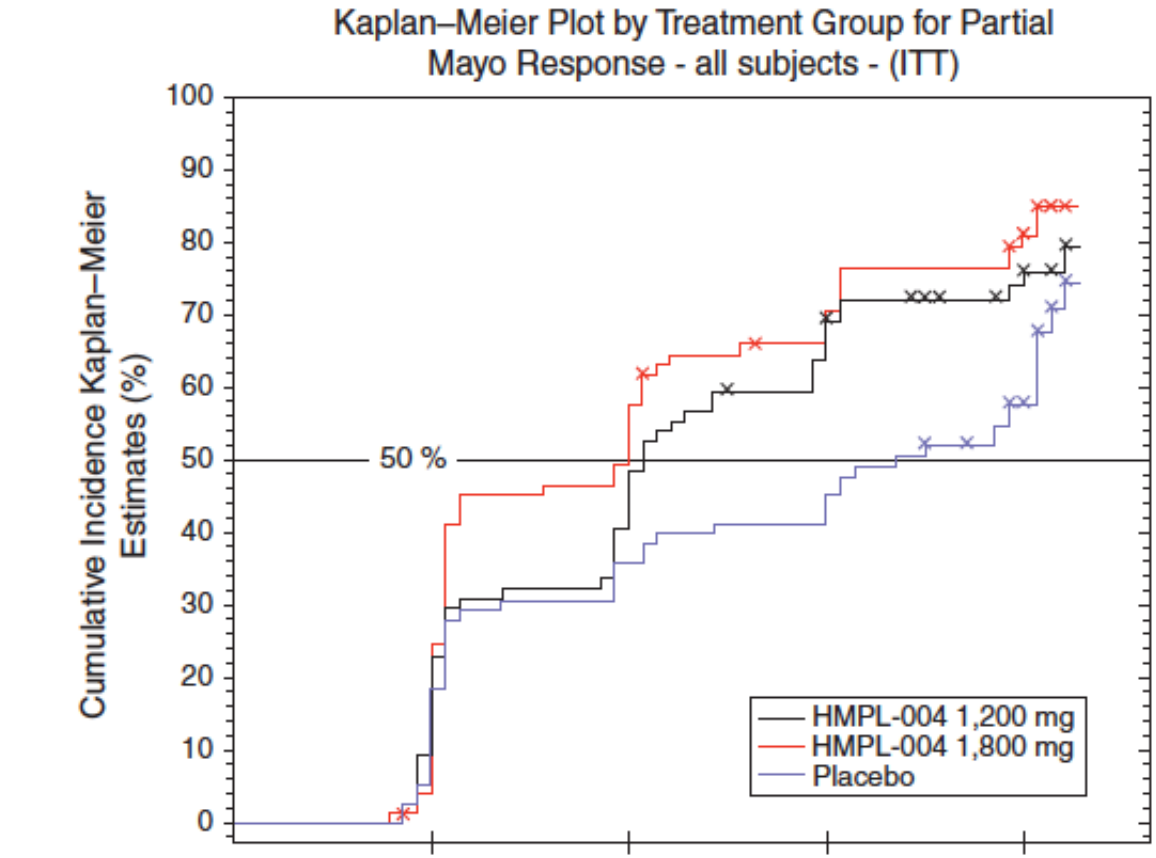
Ng, *et al* (2013). *Aliment Pharm Ther*

Efficacy of Herbal Therapies in UC

Author, reference	Country	Year	CAM	Number of subjects	Comparator	Duration	Remission/ Response on CAM (%)	Remission/ Response on comparator (%)
Langmead[21]	UK	2004	Aloe vera	44	Placebo	4 weeks	30	7
Ben-Arye[22]	Israel	2002	Triticum aestivum	23	Placebo	4 weeks	91	42
Khan[23]	UK	2002	Bovine colostrum enema	14	Placebo	4 weeks	–	–
Sandborn[33]	5 countries in the USA and Europe	2013	HMPL-004	224	Placebo	8 weeks	38 60	25 40
Fukunaga[35]	Japan	2013	Xilei-san suppository	30	Placebo suppository	2 weeks	46	0
Zhang[34]	China	2013	Xilei-san enema	35	Dexamethasone enema	8 weeks	–	–
Tang[25]	China	2010	HMPL-004	120	Mesalazine	8 weeks	21	16
Gupta[24]	India	2001	Boswellia serrata	30	Sulphasalazine	6 weeks	70	40
Chen[26] (article in Chinese)	China	1994	Jian Pi Ling (JPL) tablet	153	Sulphasalazine (S), Placebo (P)	90 days	53	28 (S) 19 (P)
Wang[27]	China	1997	Kui Jie Qing enemas	106	Sulphasalazine, oral prednisolone, prednisolone enema	20 days	72	9
Chen[28]	China	1999	Yukui tang tablets	118	Oral prednisolone, neomycin and vitamin B	40 days	33	17

Ng, *et al* (2013). *Aliment Pharm Ther*

Andrographis paniculata Extract (HMPL-004)



Subjects at Risk:	Week 2	Week 4	Week 6	Week 8
Andrographis paniculata - 1,200 mg	74	57	38	21	11
Andrographis paniculata - 1,800 mg	74	55	31	20	10
Placebo	75	61	48	41	17

- Asian herbal extract with anti-inflammatory effects TNF, IL-1β, and NF-κB
- RCT multicenter trial
- Patients with mild – moderate UC on 5-ASA or no therapy
  - N=224 patients
- Clinical response, but not remission, achieved at week 8

Sandborn, *et al* (2013). *AJG*

Curcumin in IBD

- LMW hydrophobic polyphenol that is extracted from turmeric
- Inhibits cytokine – mediated NF-κB activation
- One RCT double-blind, multicenter trial in UC
  - N = 89 total
  - 5-ASA +/- curcumin for 6 months
  - Clinical activity and endoscopic indices
  - Disease relapse: 5% vs. 21% ($p < 0.04$) in 6 months

Jobin, *et al* (1999). *J Immunol*
Hanai, *et al* (2006). *Clin Gastro Hepatol*
Suskind, *et al* (2013). *JPGN*

Curcumin is Well-Tolerated in Pediatric IBD Patients

Patient no.	Sex/age, y	Diagnosis	Baseline/9-wk PUCAI or PCDAI	Laboratory changes during study*	Concomitant medications	Finished study
1	Male/14	UC	0/0	None	Anti-TNF antibody therapy	Yes
2	Female/14	Crohn disease	0/0	None	Anti-TNF antibody therapy	Yes
3	Male/14	Crohn disease	0/0	None	Anti-TNF antibody therapy and mesalamine	Yes
4	Male/17	Crohn disease	0/0	None	Anti-TNF antibody therapy	Yes
5	Female/11	UC	30/0	None	Mesalamine therapy	Yes
6	Female/13	UC	25	None	Mesalamine therapy	No
7	Female/18	Crohn disease	0/0	None	Anti-TNF antibody therapy	Yes
8	Male/15	Crohn disease	0/0	None	Mesalamine therapy	Yes
9	Male/12	UC	0	None	Anti-TNF antibody therapy	No
10	Male/18	Crohn disease	5/0	None	Mesalamine therapy	Yes
11	Male/15	UC	25/5	None	Mesalamine therapy	Yes

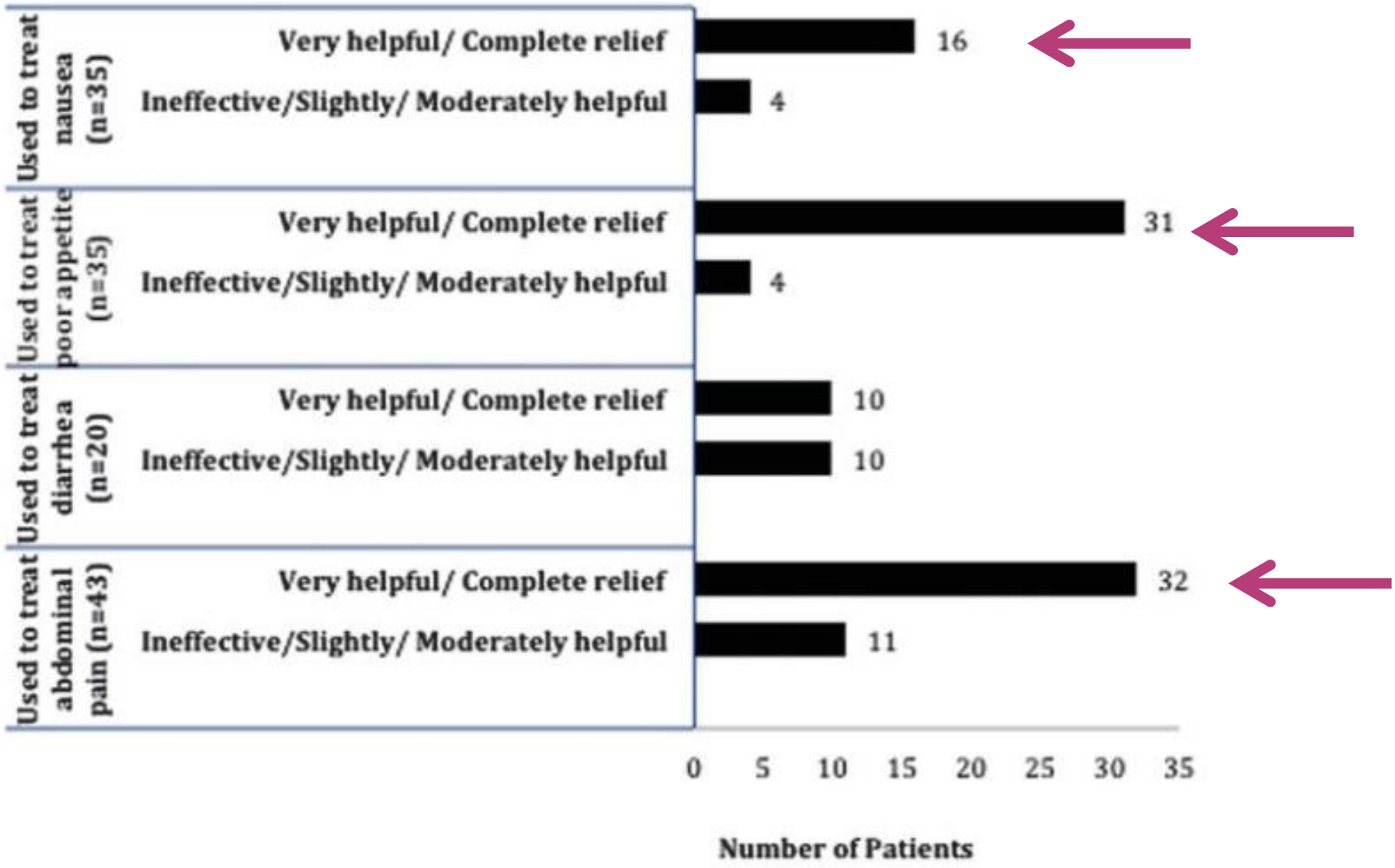
PCDAI = Pediatric Crohn's Disease Activity Index; PUCAI = Pediatric Ulcerative Colitis Activity Index; TNF = tumor necrosis factor; UC = ulcerative colitis.

* Laboratories evaluated include complete blood count, C-reactive protein, albumin, amylase, alanine transaminase, and creatinine.

- Tolerability established for pediatric IBD patients
  - Doses increased in 3 week intervals
  - 3/11 with improved PUCAI/PCDAI

Suskind, *et al* (2013). *JPGN*

Cannabis Usage in IBD



Allegretti, *et al* (2013). *Inflamm Bowel Dis*

Cannabis Usage in IBD

- Increased interest in utilizing as primary and/or adjunct therapy for IBD
- Primary mode of delivery: inhalation
- Factors associated with usage:
  - Younger age (<25 yr)
  - Frequent user for longer duration
  - Need for acute symptom relief
- Positive impact on GI symptoms; however, predictor (OR 5.03) for progression to surgery

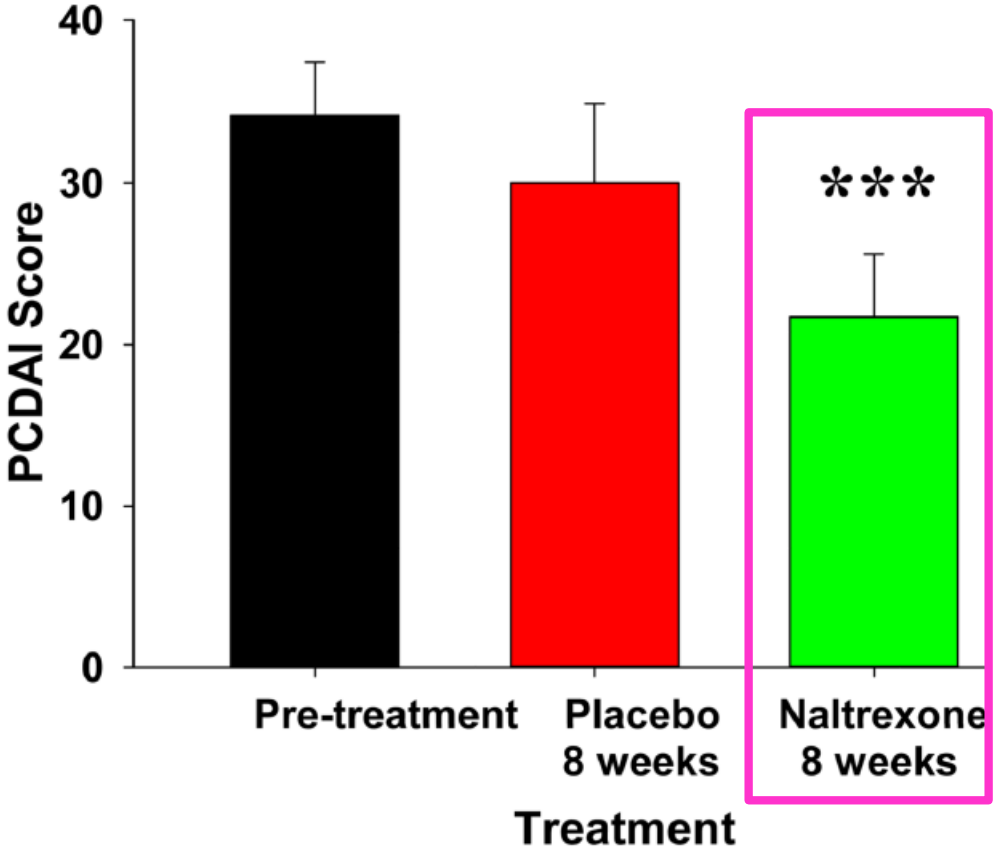
Storr, *et al* (2014). *Inflamm Bowel Dis*

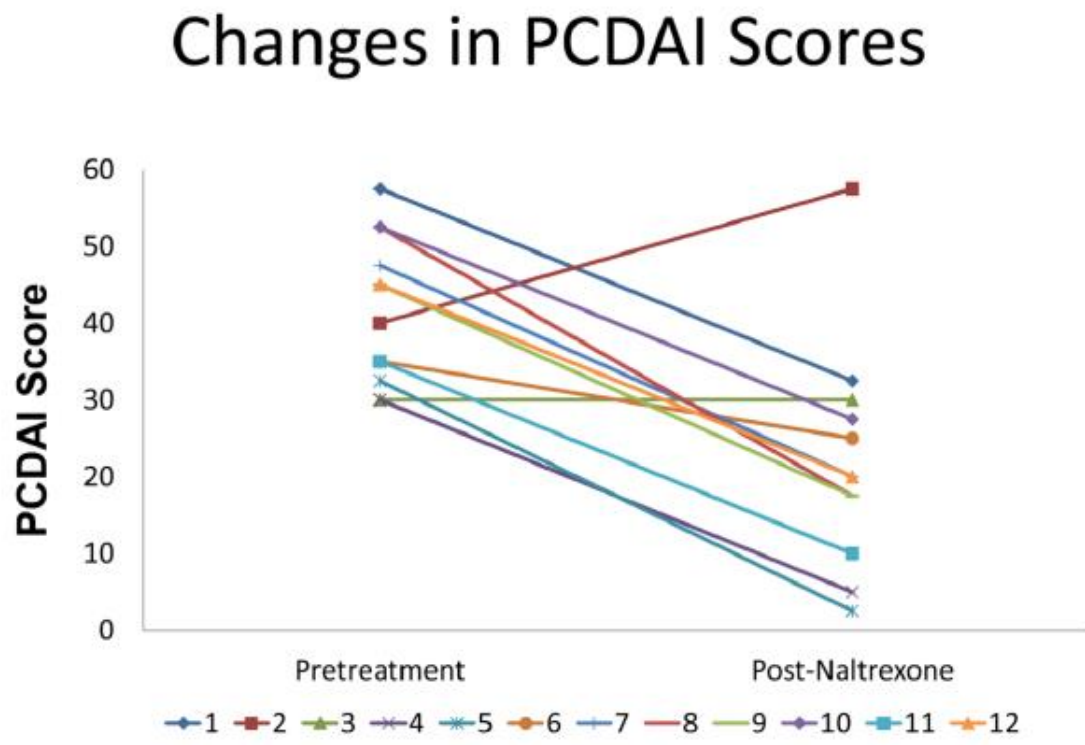
Low-Dose Naltrexone in Crohn's Disease

- Non-selective opioid receptor antagonist that interacts with all three opioid receptors subtypes
- May regulate immune responses →cytokines and chemokines
- Children with moderate – severe Crohn's disease
  - N = 12
  - Stable on 5-ASA (4 weeks) or IM (12 weeks)
  - 8 weeks with LDN (0.1 mg/kg) or placebo, then 8 weeks with LDN
  - Outcomes: PCDAI and QOL

Smith, *et al* (2007). *AJG*

Low-Dose Naltrexone in Crohn's Disease



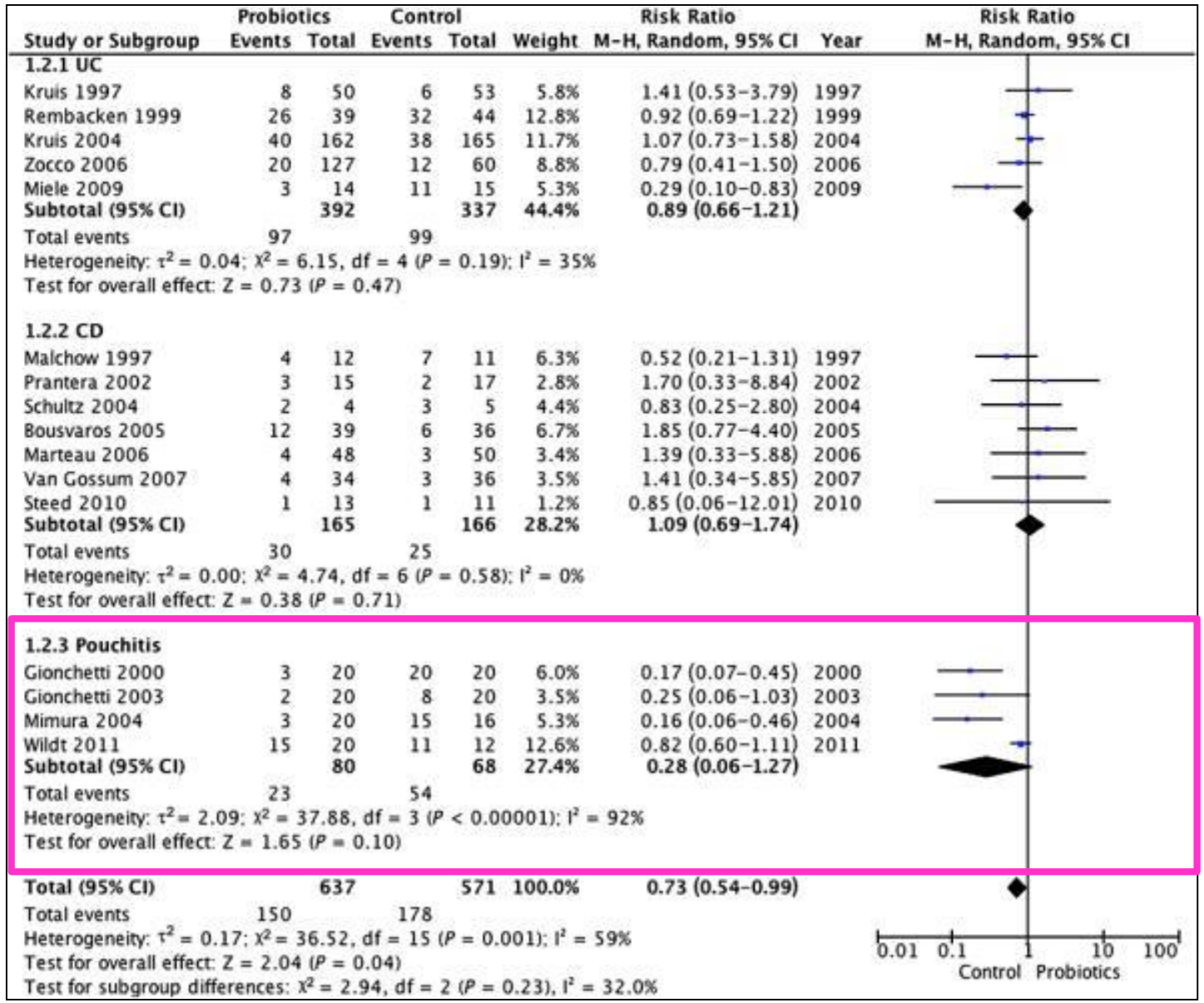


Smith, *et al* (2007). *AJG*

Therapeutic Manipulation of Microbiota

- Probiotics
  (Gionchetti, *et al.* 2000; Bousvaros, *et al.* 2005, Rahimi, *et al*. 2008; Sood, *et al.* 2009)
  - Some efficacy in pouchitis, UC but not Crohn's
  - Potential of butyrate producing organsims
- Fecal bacteriotherapy
  (Bennet, *et al.* 1989, Borody, *et al*. 2003, 2011; Duplessis, *et al.* 2012)
  - Effective in *C. difficile* infection
  - Limited studies in IBD; potential in UC
  - Dosing intervals; method of administration; pre-treatment
- Dietary intervention
  (Wu, *et al.* 2011; Devkota, *et al*. 2012; Duboc, *et al.* 2012)
  - Dietary fiber and SCFA
  - Dietary fat and bile acid metabolism

Probiotic Efficacy in IBD



Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.2.1 UC							
Kruis 1997	8	50	6	53	5.8%	1.41 (0.53–3.79)	1997
Rembacken 1999	26	39	32	44	12.8%	0.92 (0.69–1.22)	1999
Kruis 2004	40	162	38	165	11.7%	1.07 (0.73–1.58)	2004
Zocco 2006	20	127	12	60	8.8%	0.79 (0.41–1.50)	2006
Miele 2009	3	14	11	15	5.3%	0.29 (0.10–0.83)	2009
Subtotal (95% CI)		**392**		**337**	**44.4%**	**0.89 (0.66–1.21)**	
Total events	97		99				
Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 6.15$, df = 4 ($P = 0.19$); $I^2 = 35\%$							
Test for overall effect: Z = 0.73 ($P = 0.47$)							
1.2.2 CD							
Malchow 1997	4	12	7	11	6.3%	0.52 (0.21–1.31)	1997
Prantera 2002	3	15	2	17	2.8%	1.70 (0.33–8.84)	2002
Schultz 2004	2	4	3	5	4.4%	0.83 (0.25–2.80)	2004
Bousvaros 2005	12	39	6	36	6.7%	1.85 (0.77–4.40)	2005
Marteau 2006	4	48	3	50	3.4%	1.39 (0.33–5.88)	2006
Van Gossum 2007	4	34	3	36	3.5%	1.41 (0.34–5.85)	2007
Steed 2010	1	13	1	11	1.2%	0.85 (0.06–12.01)	2010
Subtotal (95% CI)		**165**		**166**	**28.2%**	**1.09 (0.69–1.74)**	
Total events	30		25				
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 4.74$, df = 6 ($P = 0.58$); $I^2 = 0\%$							
Test for overall effect: Z = 0.38 ($P = 0.71$)							
1.2.3 Pouchitis							
Gionchetti 2000	3	20	20	20	6.0%	0.17 (0.07–0.45)	2000
Gionchetti 2003	2	20	8	20	3.5%	0.25 (0.06–1.03)	2003
Mimura 2004	3	20	15	16	5.3%	0.16 (0.06–0.46)	2004
Wildt 2011	15	20	11	12	12.6%	0.82 (0.60–1.11)	2011
Subtotal (95% CI)		**80**		**68**	**27.4%**	**0.28 (0.06–1.27)**	
Total events	23		54				
Heterogeneity: $\tau^2 = 2.09$; $\chi^2 = 37.88$, df = 3 ($P < 0.00001$); $I^2 = 92\%$							
Test for overall effect: Z = 1.65 ($P = 0.10$)							
Total (95% CI)		**637**		**571**	**100.0%**	**0.73 (0.54–0.99)**	
Total events	150		178				
Heterogeneity: $\tau^2 = 0.17$; $\chi^2 = 36.52$, df = 15 ($P = 0.001$); $I^2 = 59\%$							
Test for overall effect: Z = 2.04 ($P = 0.04$)							
Test for subgroup differences: $\chi^2 = 2.94$, df = 2 ($P = 0.23$), $I^2 = 32.0\%$							

Shen, *et al* (2014).*Inflamm Bowel Dis*

Fructo-Oligosaccharides in Crohn's

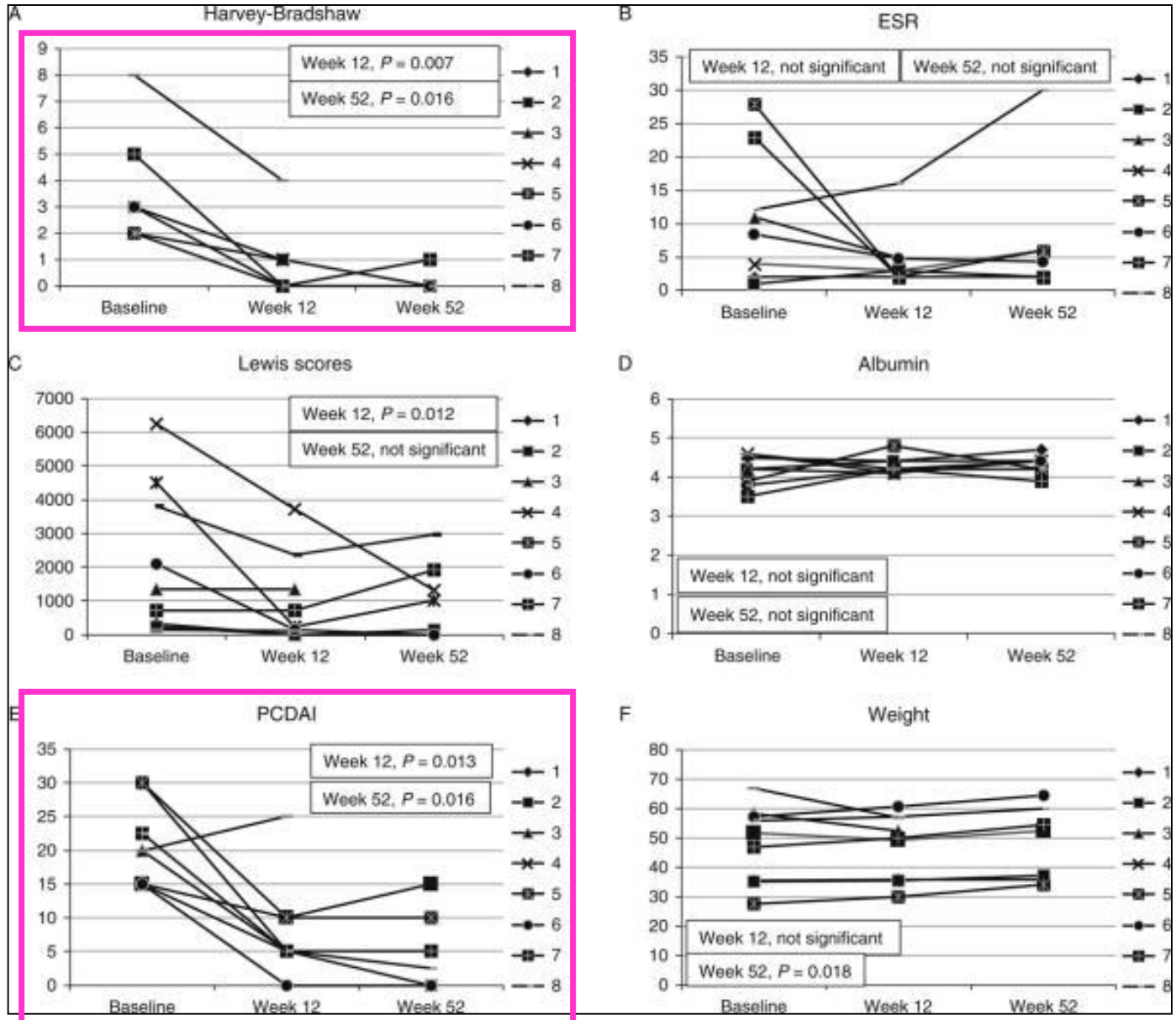
Table 2 Response and remission rates in the fructo-oligosaccharide (FOS) and placebo groups

	FOS	Placebo	p Value
Response*			
Intention to treat, n (%)	12 (22%)	19 (39%)	0.067
Per protocol, n (%)	12 (30%)	19 (42%)	0.243
Remission†			
Intention to treat, n (%)	6 (11%)	10 (20%)	0.193
Per protocol, n (%)	6 (15%)	10 (22%)	0.395

- No significant difference in clinical response
- No significant changes in fecal *Bifidobacteria spp* or *F. prausnitzii*

Benjamin, *et al*. 2011. *Gut*

Specific Carbohydrate Diet in Crohn's



Cohen, *et al* (2014). *JPGN*

Specific Carbohydrate Diet in Crohn's

Albumin levels, g/dL						
Study ID	Before diet intervention	3 mo after	6 mo after	12 mo after	15 mo after	18 mo after
1	3.2	3.9	4.2			
2	3.4	3.9	4.3			
3	3.5		4.2	4.1		4.1
4	3.8	4.5	4.3	4.5	4.3	4.3
5	3	3.2	3.8	3.4		
9	3.8		4.1			
10	3.2	4.6	4.2	4.1		

C-reactive protein, mg/dL						
Study ID	Before diet intervention	3 mo after	6 mo after	12 mo after	15 mo after	18 mo after
1	4.2	0.8	1.2			
2	2.4	0.8	0.8			
3	5.8		0.8	0.8		0.8
4	0.8	0.8	0.8	0.8	0.8	0.8
5	2.8	0.9	0.8	0.8		
9	2.1		0.8			
10	6.1	0.8	0.8	0.8		

Hematocrit (%)						
Study ID	Before diet intervention	3 mo after	6 mo after	12 mo after	15 mo after	18 mo after
1	36.3	39.9	40.1			
2	35.5	37.7	37.7			
3	35.3		38.2	42.5		42.5
4	41	41.7	40.6	39.7	37.7	39.6
5	33.9	34.9	34.6	36.7		
9	36.9		38.2			
10	42.3	45.8	47	44.5		

*For Seattle Children's laboratory normal values for albumin is between 3.8 and 5.4 g/dL; normal range for C-reactive protein <0.8; normal range for hematocrit between 34% and 40%.

Suskind, *et al* (2014).

Acupuncture in IBD

- Utilization as therapy in IBD for potential anti-inflammatory effects
- Prospective RCT in patients with mild-moderate Crohn's disease
  - N = 51 total
  - 10 treatments over 4 weeks with 12 week follow-up
- Outcomes
  - CDAI: 250 ± 51 →163 ± 56 (vs. sham; p <0.003)
  - QOL: Improved sense of well-being (p < 0.045)

Joos, *et al* (2004). *Digestion*

Hypnosis for IBD

- Case series of 8 women with IBD with reported improvement of QOL
- Hypnotherapy in ulcerative colitis
  - N = 17 patients with active UC
  - 50 minute session of hypnotherapy
  - Mucosal parameters: Substance P↓ 81% (p = 0.001); ↓mucosal blood flow 18% (p = 0.0004); ↓histamine by 35% (P=0.002)
  - Serum: ↓ IL-6 by 53% (p = 0.001) and IL-13 by 53% (p = 0.003)

Keefer, *et al* (2007). *Int J Clin Exp Hypn*
Mawdsley, *et al (*2008). *AJG*

How Should We Approach CAM in IBD?

- Be proactive and open: ask about CAM usage/interest and listen without judgment
- Understand the literature
  - Adjunct versus primary therapies
  - Recognize the potential downsides of CAM (i.e. therapy toxicities)
- Research opportunities
  - Larger scale studies
  - Delineating mechanisms and treatment efficacy
- Know your resources: local and online

Resources

- AAP Section on Integrative Medicine
  - http://www2.aap.org/sections/chim/
- Arizona Center of Integrative Medicine
  - http://integrativemedicine.arizona.edu/education/peds_imr.html
- CCFA
  - http://www.ccfa.org/resources/complementary-alternative.html
- NIH National Center on Complementary and Alternative Medicine (NCCAM)
  - http://nccam.nih.gov