AHC Media

Integrative Medicine

Evidence-based summaries and critical reviews on the latest developments in integrative therapies [ALERT]

Vol. 17, Issue 7, July 2014
www.ahcmedia.com

GASTROINTESTINAL DISEASE

Probiotics for Gastrointestinal Intervention: What About Direct Delivery?

By Luke Fortney, MD, and Rian Podein, MD

Dr. Fortney is a physician with Meriter Medical Group, Madison, WI. Dr. Podein is a family physician, Group Health Cooperative of South Central Wisconsin, Madison, WI.

Dr. Fortney and Dr. Podein report no financial relationships relevant to this field of study.

Probiotics are defined by the World Health Organization as live microorganisms that, when administered in adequate amounts, confer a health benefit.[1] Probiotics are available in "functional foods" that contain live active cultures of various bacterial species — such as yogurt, sauerkraut, tempeh, kombucha, and others — or as dietary supplements in the form of capsules, tablets, and powders. Governmental regulation in the United States depends on the product's intended use: a food ingredient, dietary supplement, or a drug.

Interest in probiotics has proven to be a growth industry for both consumers and the supplement industry. In 2011, U.S. sales of probiotic supplements totaled nearly $770 million and they continue to be one of the fastest growing dietary supplements.[2] Since the early 20th century when Russian Nobel Laureate Elie Metchnikoff first proposed the idea of ingesting microbes for health benefits, there has been ongoing investigation into both the basic and applied clinical sciences.[3] The National Institutes of Health launched the Human Microbiome Project in 2008 with the mission to identify and characterize the microbial communities that inhabit both healthy and unhealthy people.

PROBIOTIC CLINICAL RESEARCH

More than 100 trillion microbes reside within the human gastrointestinal (GI) tract. This GI microbiota is acquired at birth and develops quickly during the early newborn period with subsequent windows of susceptibility and alteration throughout childhood development

Financial Disclosure: *Integrative Medicine Alert*'s executive editor David Kiefer, MD, peer reviewer J. Adam Rindfleisch, MD, MPhil, AHC Media executive editor Leslie Coplin, and managing editor Neill Kimball report no financial relationships relevant to this field of study.

Integrative Medicine [ALERT]

Integrative Medicine Alert,
Integrative Medicine Alert (ISSN 1096-942X) is published monthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.

Periodicals Postage Paid at Atlanta, GA, and at additional mailing offices.

GST Registration Number: R128870672.
POSTMASTER: Send address changes to *Integrative Medicine Alert*, P.O. Box 550669, Atlanta, GA 30355.

SUBSCRIBER INFORMATION
1-800-688-2421
customerservice@ahcmedia.com
www.ahcmedia.com

Questions & Comments:
Please contact Executive Editor **Leslie Coplin**, at leslie.coplin@ahcmedia.com

Subscription Prices
United States
Print: 1 year with free *AMA PRA Category 1 Credits™*: $319
Add $19.99 for shipping & handling.
Online only: 1 year (Single user) with ***free*** *AMA PRA Category 1 Credits™*: $269

Multiple Copies: Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

Back issues: $42. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION
AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of *2.0 AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The American Osteopathic Association has approved this continuing education activity for up to 2.0 AOA Category 2-B credits.

This CME activity is intended for physicians and researchers interested in integrative medicine. It is in effect for 36 months from the date of the publication.

AHC Media

prior to the establishment of a relatively stable "adult" gut microbiota.[4] This established gut ecosystem can shift due to influences such as aging, diet, geographical location, intake of food supplements and medications, infectious disease, chronic illness, and likely other yet unknown factors.[5] There is increasing evidence to support an association between the composition of the human microbiome and a wide range of diseases, including *Clostridium difficile* infection (CDI), irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), colonization with multidrug-resistant organisms, cancer, osteoporosis, cardiovascular disease, obesity, allergic diseases, autoimmune disorders, and neuropsychiatric illnesses.[5,6,7,8] However, ongoing research and therapy challenges include what probiotic strains should be used for what conditions, in which people, for how long, and at what dose and type of delivery.

IBS AND OTHER GUT DISORDERS

The prevention and treatment of various GI disorders by manipulation of the microbial ecosystem with orally administered probiotics has been widely studied with varying strengths of evidence. However, overall the strongest evidence for use of probiotics includes GI-related disorders such as IBS, IBD, CDI, antibiotic-associated diarrhea (AAD), and various other forms of infectious diarrhea.[9,10] Unfortunately, there have been significant limitations and variation among studies that raise many more questions regarding efficacy, viability, optimal species and genus selection for specific conditions in specific people, single vs combination products, optimal colony forming units dosing, and adequate treatment duration.[11]

Although incompletely understood, purported mechanisms of benefit from probiotics use include the direct remodeling of microbial communities, competition to/suppression of pathogens, enhanced immune function/modulation, up-regulation of anti-inflammatory factors, suppression of pro-inflammatory factors, and proliferation and promotion of intestinal epithelial barrier function.[10] Interestingly, however, few studies have actually documented the survival of orally administered probiotics after passage through the caustic upper GI tract environment. Further, probiotic effects have been demonstrated using both viable and non-viable bacteria.[12,13] What's more, colonization of the GI tract from orally administered probiotics appears to be temporary at best, with noted disappearance of introduced strains from the stool soon after discontinuation. In general, oral probiotics appear to have their effects via regulating the function — including gene expression and metabolism — of the already established GI microbiota ecosystem, rather than actually changing the existing microbial composition itself.[14]

Pursuit of the modulation of intestinal microflora is an intuitive therapy for many gut disorders. Foremost is IBS, which involves disruption of the colonic microbiota in various ways. There are various manifestations of IBS, such as constipation, diarrhea, bloating, and mixed symptom variations. Overall, IBS is a heterogeneous disorder characterized by abnormal GI motility, altered GI microbiota composition, low-grade chronic inflammation, visceral hypersensitivity and hyperalgesia, and disruption of the gut-brain communication axis. However, specific identification of biologic markers based on genetic polymorphisms remains undetermined and inconsistent.[15] It is also important to keep in mind that IBS is a functional bowel disorder with many contributing factors, including a significant association with adult and childhood abuse and trauma. The pathogenesis of IBS is multidimensional and is heavily influenced by biopsychosocial dysfunction in various forms. Stress, although not considered a cause of IBS, is nonetheless a significant trigger that is often present with IBS flares for many patients.[15]

Summary Points

- Probiotic therapies appear to be safe and may be helpful for various health problems.
- The strongest evidence is for use as an adjunctive supportive therapy for gastrointestinal-related disorders.
- Although direct colonic probiotic delivery therapies appear promising, further research is needed.

Specifically regarding altered gut microbiota, there does appear to be a consistent theme of reduced Bacteroides and increased Firmicutes strains in IBS,[16] but actual characterization of individual gut flora remains difficult and inconsistent. Nonetheless, research suggests that targeted treatment using certain antibiotics and select probiotics based on individual differences in intestinal microbiota composition may be effective in alleviating IBS symptoms.[16] A recent meta-analysis reported that overall, all probiotic species and strains appear to improve flatulence and bloating in patients with IBS compared with placebo.[17] Two other meta-analyses concluded that probiotics in general improve overall IBS symptoms for most patients.[17] However, one RCT found no significant benefit from using a multispecies probiotic oral supplement for 6 weeks among 35 patients diagnosed with IBS. In this placebo-controlled trial, visceral hypersensitivity decreased significantly for both the probiotic group as well as the control group, but overall pain scores and mean symptom scores did not differ.[18]

When it comes to iatrogenic AAD, one study found that older hospitalized patients being treated with antibiotics for various reasons were less likely to contract AAD when given *Lactobacillus paracasei* fermented milk prophylactically. This was also found to be very cost effective, with a total estimated cost savings of more than $575 per hospitalized patient > 65 years of age, which is a particularly vulnerable demographic.[19] This finding is consistent overall in terms of using probiotics for the prevention of gut-associated disorders of nearly every kind, noting that one study concluded an average risk reduction of 35% compared to placebo in maintaining gut homeostasis for various GI conditions.[20]
In more severe disease states, such as IBD, altered gut microbiota — also called dysbiosis — appears to be a key player in the prolonged and stubborn course of these disorders. Several studies have found an association with polymorphisms in genes that are involved in autophagy — a process that involves cell degradation of unnecessary or dysfunctional cellular components that helps maintain healthy cells — which is thought to be a result of the innate relationship of host cells with adjacent luminal gut bacteria. The inverse also appears to be true, that specific gut pathogens may have a negative impact on the gut microbiome, which in turn generate protracted inflammation and immune dysfunction, which may result in the pathogenesis of IBD.[21]

In the setting of pouchitis among patients who underwent restorative proctocolectomy for various reasons including severe IBD, prolonged probiotic administration appears to be helpful. In a study of 43 randomized patients given a daily probiotic consisting of *L. acidophilus*, *delbrueckii*, *bulgaricus*, and *Bifidobacterium bifidus* for 9 months, the average severity and incidence of pouchitis decreased significantly compared to placebo. Objective biomarkers for pouchitis were also lower in the treatment group, noting lower levels of fecal pyruvate kinase and calprotectin. This study also demonstrated that long-term probiotic use is safe and effective in preventing pouchitis episodes.[22]

FECAL TRANSPLANTATION

Microbiota restorative therapies, such as fecal microbiota transplantion (FMT), provide direct anatomical delivery of various healthy microbial species to diseased or dysfunctional colons. While FMT has yet to be fully approved by the FDA, it is permitted for use in select patients for the treatment of recurrent and treatment refractory CDI. Risk of recurrence of CDI is high with use of oral antibiotics such as vancomycin and metronidazole, particularly in recurrent disease. Despite use of new novel antibiotics, such as fidaxomicin, the threat of growing resistance continues. For this and other reasons, FMT is attracting increased attention from physicians and patients alike. There are currently more than 500 case reports of FMT for the treatment of CDI, with greater than 91% efficacy.[7,23]

Given its impressive success with severe CDI, there is growing interest for the use of FMT for additional GI disorders such as IBS and IBD, as well as other "extra-intestinal" conditions such as diabetes, obesity, multiple sclerosis, and idiopathic thrombocytopenic purpura among many others.[24] While the potential application of

FMT is expanding, there are concerns for risk of inadvertent transmission of various pathogens and infectious diseases. Appropriate donor selection, standardization of donor stool preparation, insurance reimbursement, and long-term safety and efficacy are ongoing concerns.[7] Additionally, there is a general cultural aversion to the idea of "stool sharing." Ideally, a clearer understanding of the optimal probiotics composition for specific disorders will likely lead to strategic microbiota "mining" from healthy donor stool samples vs production and selection of various specific bacterial strains in microbiology laboratories without the need for and potential risks of FMT.

DIRECT COLONIC PROBIOTIC DELIVERY

Concurrent with the rising interest in FMT is the more facile idea of direct colonic delivery of probiotic supplements, in single or combination strains. The direct anatomical delivery of probiotics has also been explored in oral and vaginal disorders with some reported benefit.[25,26] However, research into the rectal application of probiotic supplements for GI disorders has been largely absent with the exception of a few small trials of an enema supplied single-species probiotic for ulcerative colitis, which was well tolerated and showed some benefit.[27,28]

For gut-related disorders, such as IBS and AAD (and likely others), the direct delivery of multistrain probiotics is a reasonable, safe, inexpensive, and effective adjunctive therapy to standard of care. Furthermore, it circumvents the challenge of orally administered probiotic destruction by the caustic upper GI environment. Although research supporting direct colonic probiotic delivery (DCPD) use is surprisingly lacking, anecdotal evidence and case reports are promising. In the clinical setting, for non-immunocompromised patients who struggle with various GI-related disorders but who find only limited success from standard of care therapies, it is reasonable to recommend DCPD as an adjunctive therapy option when prescribed with careful and clear instruction for proper use.

DCPD should use a saline solution transport medium, which is the preferred delivery agent for FMT.[29] While further research is needed, this approach has been used successfully and safely in the clinic setting. In addition to implementing a healthy diet and regular exercise (see www.meriter.com/wellness for exercise and nutrition prescriptions), DCPD can be considered and used under clinical supervision with properly screened patients who are willing and able (*see Table 1*).

Table 1. How to Arrange a Probiotic Fleet Enema at Home

- Avoid use if feeling ill (fever, chills, sweats, current use of corticosteroids, or recent GI procedure).
- This is best used after a bowel movement to allow better retention and distribution of the multistrain probiotic saline solution.
- Obtain one saline Fleet enema (133 mL, or smaller 59 mL volume pediatric version).
- Unscrew the enema applicator tip to access the saline liquid inside.
- Open and directly pour into the saline solution two probiotic capsules from three different probiotic brands/varieties (e.g., Culturelle, Florajen3, VSL#3, etc.) A variety of different probiotic strains is key.
- Re-apply the probiotic tip applicator, tighten, and shake the saline probiotic enema solution a few times.
- Lay down (left or right side, bent knees flexed into the abdomen) and insert the probiotic fleet enema applicator tip rectally, firmly squeeze the bottle to deliver the entire contents into the rectum, and then remove the applicator.
- Suggested body positions for improved probiotic distribution in the colon: laying on your left side, then right side, cat-cow, child pose, bridge, half shoulder stand, repeat.
- Try to retain the entire probiotic enema contents rectally (hold the probiotic enema as long as you can), but stay near a toilet.
- Repeat monthly as needed for gut symptom relief.

ADVERSE EFFECTS OF PROBIOTICS

A 2011 Agency for Healthcare Research and Quality assessment of the safety of probiotics concluded that current evidence does not suggest widespread risk or negative side effects associated with probiotics. However, the data on safety and long-term safety are limited, and the risk of serious side effects may be greater in people who have underlying health conditions.[30] Although probiotics fall under an FDA category of generally recognized as safe, or having been adequately shown to be safe for general consumption,

avoidance or close medical supervision and caution are recommended for several conditions, including immunocompromised state, premature infant patients in the neonatal period, presence of any type of intravascular catheter, impaired intestinal epithelial barriers, and advanced cardiac valve disease.[31]

CONCLUSIONS

There is accumulating evidence regarding the relationship of the GI microbiota with GI health and disease. Limitations of orally administered probiotic supplements — along with the impracticalities, cost, and concerns of inadvertently introducing pathogens through widespread FMT — support further investigation into the direct rectal delivery of various probiotic preparations (DCPD) for various GI disorders. ■

REFERENCES

1. (WHO) Joint Food and Agriculture Organization of the United Nations/World Health Organization Working Group report on drafting guidelines for the evaluation of probiotics in food, London, Ontario, Canada, April 30 and May, 2002. Available at: ftp://ftp.fao.org/es/esn/food/wgreport2.pdf. Accessed March 28, 2014.
2. Reddy S. Probiotics' benefits may be more than a gut feeling. *The Wall Street Journal* Nov. 26, 2012. Available at: http://online.wsj.com/news/articles/SB10001424127887324784404578143402702878118. Accessed March 28, 2014.
3. Podolsky SH. Metchnikoff and the microbiome. *Lancet* 2012;380:1810-1811.
4. Petschow B et al. Probiotics, prebiotics, and the host microbiome: The science of translation. *Ann N Y Acad Sci* 2013;1306:1-17.
5. Bäckhed F, et al. Defining a healthy human gut microbiome: Current concepts, future directions, and clinical applications. *Cell Host Microbe* 2012;12:611-622.
6. Mai V, et al. Recent advances and remaining gaps in our knowledge of associations between gut microbiota and human health. *World J Gastroenterol* 2009;15:81-85.
7. Khanna S, Tosh PK. A clinician's primer on the role of the microbiome in human health and disease. *Mayo Clin Proc* 2014;89:107-114.
8. Parvaneh K, et al. Effect of probiotics supplementation on bone mineral content and bone mass density. *Scientific World J* 2014;ePub doi: 10.1155/2014/595962.
9. Goldin BR, Gorbach SL. Clinical indications for probiotics: An overview. *Clin Infect Dis* 2008;46(Suppl 2):S96-S100.
10. Preidis GA, Versalovic J. Targeting the human microbiome with antibiotics, probiotics, and prebiotics: Gastroenterology enters the metagenomics era. *Gastroenterology* 2009;136:2015-2031.
11. Verna EC, et al. Use of probiotics in gastrointestinal disorders: What to recommend? *Therap Adv Gastroenterol* 2010;3:307-319.
12. Kailasapathy K, Chin J. Survival and therapeutic potential of probiotic organisms with reference to *Lactobacillus acidophilus* and *Bifidobacterium* spp. *Immunol Cell Biol* 2000;78:80-88.
13. Jijon H, et al. DNA from probiotic bacteria modulates murine and human epithelial and immune function. *Gastroenterology* 2004;126:1358-1373.
14. McNulty NP, et al. The impact of a consortium of fermented milk strains on the gut microbiome of gnotobiotic mice and monozygotic twins. *Sci Transl Med* 2011;3:106ra106.
15. Chang FY. Irritable bowel syndrome: The evolutiohn of multi-dimensional looking and multidisciplinary treatments. *World J Gastroenterol* 2014;20:2499-2514.
16. Hong SN, Rhee PL. Unraveling the ties between irritable bowel syndrome and intestinal microbiota. *World J Gastroenterol* 2014;20:2470-2481.
17. Cash BD. Emerging role of probiotics and antimicrobials in the management of irritable bowel syndrome. *Curr Med Res Opin* 2014 [Epub ahead of print].
18. Luddi S, et al. Randomized clinical trial on the effect of a multispecies probiotic on visceroperception in hypersensitive IBS patients. *Neurogastroenterol Motil* 2014;26:705-14.
19. Lenoir-Wijnkoop I, et al. Nutrition economic evaluation of a probiotic in the prevention of antibiotic associated diarrhea. *Front Pharmacol* 2014;5:13 dpo" 10.3389/fphar.2014.00013.
20. Vitetta L, et al. Probiotics, prebiotics and the gastrointestinal tract in health and disease. *Inflammopharmacology* 2014;22:135-154.
21. Hold GL, et al. Role of the gut microbiota in inflammatory bowel disease pathogenesis: What have we learned in the past 10 years? *World Gastroenterol* 2014;20:1192-1210.
22. Tomasz B, et al. Long term use of probiotics lactobacillus and bifidobaterium has a prophylactic effect on the occurrence and severity of pouchitis: A randomized prospective study. *Biomed Res Int* 2014;2014:208064.
23. McCune VL, et al. Faecal transplantation for the treatment of *Clostridium difficile* infection: A review. *Int J Antimicrob Agents* 2014;43:201-206.
24. Smits LP, et al. Therapeutic potential of fecal microbiota transplantation. *Gastroenterology* 2013;145:946-953.
25. Stamatova I, Meurman JH. Probiotics: Health benefits in the mouth. *Am J Dent* 2009;22:329-338.
26. Mastromarino P, et al. Bacterial vaginosis: A review on clinical trials with probiotics. *New Microbiol* 2013;36:229-238.
27. Oliva S, et al. Randomised clinical trial: The effectiveness of *Lactobacillus reeuteri* ATCC 55730 rectal enema in children with active distal ulcerative colitis. *Aliment Pharmacol Ther* 2012;35:327-334.
28. Matthes H, et al. Clinical trial: Probiotic treatment of acute distal ulcerative colitis with rectally administered *Escherichia coli* Nissle 1917 (EcN). *BMC Complement Altern Med* 2010;10:13.
29. Borody TJ, et al. Fecal microbiota transplantation: Indications, methods, evidence, and future directions. *Curr Gastroenterol Rep* 2013;15:337.
30. Hempel S et al. Safety of Probiotics to Reduce Risk and Prevent or Treat Disease. Evidence Report/Technology Assessment no. 200. Agency for Healthcare Research and Quality Web site. Available at: www.ahrq.gov/clinic/tp/probiotictp.htm. Accessed May 13, 2014.
31. Floch MH. Probiotic safety and risk factors. *J Clin Gasteroenterol* 2013;47:375-376.

ABSTRACT & COMMENTARY

Dietary Fats and Heart Health: Big Numbers, but Questions Linger

By Howell Sasser, PhD

Associate, Performance Measurement, American College of Physicians, Philadelphia, PA

Dr. Sasser reports no financial relationships relevant to this field of study.

SYNOPSIS: A meta-analysis and a clinical trial, both published recently, found that the evidence of cardiovascular benefit with increased consumption of omega-3 fatty acids is weak at best. Large study samples make these results compelling, but caution is warranted in interpreting and applying them in practice.

SOURCES: Chowdhury R, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk: A systematic review and meta-analysis. *Ann Intern Med* 2014;160:398-406.

AREDS2 Writing Group. Effect of long-chain omega-3 fatty acids and lutein + zeaxanthin supplements on cardiovascular outcomes: Results of the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA Intern Med* 2014;174: 763-771.

Chowdhury and colleagues conducted a systematic review of evidence published before July 2013. They identified 32 observational and 27 experimental studies that reported the risk of coronary disease associated with measured levels of circulating fatty acids or with fatty acid supplementation.

The observational studies included dietary surveys and assessment of fatty acid levels in blood (measured in whole blood, plasma, serum, or red blood cells, depending on the study) or adipose tissue. Follow-up was between 5 and 23 years. All were judged to be of high or medium quality, and all adjusted for a number of potential confounders, including age, sex, tobacco use, history of diabetes, and blood pressure. The experimental studies included dietary and supplement-based interventions. All included random assignment in their designs. The outcome of interest, risk of coronary disease, was constructed as a composite endpoint composed of fatal or non-fatal myocardial infarction (MI), coronary heart disease, coronary insufficiency, coronary death, angina, and angiographic coronary stenosis.

Meta-analytic regression models were used to produce risk estimates aggregated over all studies. Separate sets of models were produced for observational studies of circulating fatty acids (OBS-C), observational studies of dietary fatty acid intake, and interventional studies. The "population" of each model varied by the number of studies that reported a specific fatty acid, ranging between 140,000 and 420,000 person-years in the observational studies, and between 7100 and 23,000 participants in the intervention studies.

The models were assessed for potential bias by stratification on sex, year of study entry, the dietary assessment tool used, duration of follow-up, how the outcome was defined (i.e., which

Summary Points

- A large meta-analysis of observational and intervention studies found weak evidence at best for a cardioprotective effect of higher consumption of omega-3 fatty acids, including EPA and DHA.
- A recent clinical trial also found no association between consumption of omega-3 fats and a number of cardiovascular events, including myocardial infarction and death from cardiac causes.
- Two recent papers have presented evidence questioning the cardioprotective value of omega-3 polyunsaturated fatty acids. These articles appear to contradict several decades of research, the results of which have entered the popular and commercial consciousness of Americans. This article summarizes both papers and assesses their findings.

Table 1. Association of Fatty Acid Levels with Coronary Disease

	Relative Risk	95% Confidence Interval
OBS-C		
α-Linolenic Acid	0.99	(0.86-1.14)
Total omega-3	0.87	(0.78-0.97)
OBS-I		
α-Linolenic Acid	0.93	(0.83-1.03)
Eicosapentaenoic acid (EPA)	0.78	(0.65-0.94)
Docosahexaenoic acid (DHA)	0.79	(0.67-0.93)
Total omega-3	0.84	(0.63-1.11)
INT		
α-Linolenic Acid	0.97	(0.69-1.36)
Total omega-3	0.94	(0.86-1.03)

OBS-C: Observational studies of circulating fatty acids
OBS-I: Observational studies of dietary fatty acid intake
INT: Interventional studies

Adapted from: Chowdhury R, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk: A systematic review and meta-analysis. *Ann Intern Med* 2014;160: 398-406.

Table 2. Association of EPA + DHA Intake with the Risk of Cardiovascular Events

	Relative Hazard	95% Confidence Interval
CVD morbidity and mortality*	0.95	(0.78-1.17)
MI/stroke/CVD death	0.99	(0.74-1.33)
MI/stroke/CVD death/ angina	1.00	(0.77-1.29)
MI/stroke/CVD death/ CHF	1.03	(0.81-1.30)
MI/stroke/CVD death/ revascularization	0.92	(0.69-1.22)

* This endpoint includes sudden death; death due to MI, CHF, or stroke; non-fatal MI; non-fatal stroke; angina; coronary and carotid revascularization; non-fatal CHF; and resuscitated cardiac arrest.
Adapted from: AREDS2 Writing Group. Effect of Long-Chain omega-3 fatty acids and lutein + zeaxanthin supplements on cardiovascular outcomes: Results of the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA Intern Med* 2014;174:763-771.

elements of the composite outcome each individual study included), and statistical factors involved in the way the models were constructed. No significant differences in the estimates were noted.

Relevant results of the various models are shown in Table 1. Reductions in cardiovascular risk with rising omega-3 consumption were generally modest. The main exceptions to the lack of statistical significance were the results for eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) when measured through dietary intake. Interestingly, the risks with rising consumption of saturated fats and trans-fats, though elevated, were also small and statistically non-significant — 1.06 (95% CI 0.86-1.30) and 1.05 (95% CI 0.76-1.44), respectively.

A second paper reports the results of a large randomized trial. The Age-Related Eye Disease Study 2 (AREDS2) was a clinical trial of dietary supplementation for the slowing of progressive blindness in older adults. Participants were enrolled on the basis of having moderate or advanced macular degeneration in at least one eye rather than on the basis of their cardiovascular health. However, potential study enrollees with existing cardiovascular disease (CVD) were eligible if their condition was judged to be "stable," and if their initial cardiac event was more than 12 months prior to enrollment.

The combination of EPA and DHA was one of the trial's experimental interventions, and the investigators collected data on cardiovascular events as well as eye data among study participants. The cardiac endpoints recorded included MI, hospitalized acute coronary syndrome, coronary artery bypass surgery, hospitalized congestive heart failure, unexpected death, resuscitated cardiac arrest, cardiac angioplasty or stent placement, cardioverter-defibrillator placement, transient ischemic attack, ischemic or hemorrhagic stroke, or carotid artery stenting, angioplasty, or endarterectomy. Several composite endpoints were designated before the trial began, as shown in Table 2.

The study enrolled 4203 participants who were randomly assigned in a factorial fashion to EPA+DHA (350 mg and 650 mg per day,

respectively) plus placebo, another active intervention (lutein + zeaxanthin) plus placebo, both active agents, or double placebo. The median age at enrollment was 74 (range 50-85). The median duration of treatment — and of follow-up — was 4.8 years.

Table 2 shows the risk of cardiovascular events among those receiving EPA+DHA as compared with all others in the study (those receiving lutein + zeaxanthin plus placebo, and those receiving double placebo). Results for the main outcome (CVD morbidity and mortality) were similar when the analysis was restricted to a comparison of those receiving both interventions with those receiving neither (relative hazard = 0.89; 95% CI, 0.67-1.19).

■ COMMENTARY

These findings are compelling, if for no other reason, because of the large sample sizes and rigorous methods of the studies that produced them. However, there are some issues that one should bear in mind before deciding how to act on them.

The first relates to the timing and duration of "treatment" and the likely trajectory of its effects. Most, but not all, scientific studies are designed to show the time-limited (< 10 years) effects of time-limited therapies. This leads to a bias toward interventions that produce changes large enough to be measurable in a short time. In the case of dietary fats and heart disease, this seems problematic. There is evidence that fatty streaks in the arteries develop in adolescence and plaques begin to form in young adulthood.[1,2] A dietary change introduced in mid-life may not have the same effect as one begun at a young age and maintained over time. More to the point, its impact may not be measured accurately in a study which lasts only a few years, regardless of where in the life course the study takes place. Interestingly, the findings of prominent long-term longitudinal studies that have included dietary measurements have been divided on the value of omega-3 fats — the Chicago Western Electric and Nurses' Health Studies showed protective effects, but the Health Professionals' Follow-Up and Physicians' Health Studies did not.[3-6] Diet is a lifelong "process," as are its effects. Even studies that are careful to recruit only those who are free of (clinical) CVD at baseline have serious issues with bias if the average age of those recruited is in the typical clinical CVD window.

A second issue relates to the place of omega-3 fats in the totality of the diet. It is arguably the case that a key assumption of diet research involves the role of omega-3s as markers for broader eating patterns. This can take two forms. One is the assumption that those who consume higher amounts of these fats also consume higher amounts of other desirable foods (whole grains, fruits and vegetables, low-fat protein) and lower amounts of undesirable foods (refined grains, high-fat meat and dairy, refined sugar). The second form assumes that omega-3-rich foods crowd out other less desirable protein sources (in other words, tuna steak replaces cheeseburgers in an otherwise unchanged volume of protein consumption).

These premises may be valid in some cases, but there is evidence that they are not always so. A recent study found that statin users consume more calories and fat on average than non-users, and that statin users' consumption of calories and fat has increased over the past 15 years (i.e., within-group change) while non-users consumption has not changed markedly.[7] It seems reasonable to ask if a similar pattern has taken place with respect to omega-3 consumption as it has become popularized and commercialized. If getting a daily dose of omega-3s, perhaps in the form of fish oil capsules, is seen as inoculation against the effects of less healthy foods, an omega-3-rich diet may not equate to a generally healthy diet.

The total diet is also important in connection with omega-3s' hypothesized mechanism of action. It is known that omega-3 and omega-6 fats "compete" to form eicosanoids, short-lived compounds with both beneficial and harmful (specifically inflammatory) effects.[8] There is evidence that eicosanoids formed from metabolism of omega-3s are anti-inflammatory (or at least less inflammatory), so the ratio of omega-3 to omega-6 fats may have consequences for the condition of tissues such as vascular endothelium which in turn play a role in cardiovascular disease. This means that intake of EPA and DHA cannot be viewed in isolation, but rather must be considered in proportion to omega-6 intake. Risk data for varying omega-3/omega-6 ratios were not reported by either paper.

Additional cautions apply specifically to the AREDS2 Study. We should note that it was designed and powered to test the effect of an intervention on a different disease process. Even though a cardiovascular endpoint was defined before the study began, there may have been too few events to produce a statistically convincing finding. The authors do not report any post-hoc

power calculations, so we do not know if or to what extent the study was underpowered for its cardiovascular outcomes. The enrollment criteria related to CVD also appear to have been quite lenient — "stable" disease covers a wide range of types and severities of pathology. For these reasons, the AREDS2 results are best viewed as suggestive but not conclusive.

Less as a limitation than a source of speculation is the difference in findings by Chowdhury's group between total omega-3 and EPA and DHA. EPA and DHA were borderline-significant in the dietary analyses and showed greater risk reductions than total omega-3. This suggests that EPA and DHA have different — and perhaps more desirable — effects than other fatty acids in the same class. Had the AREDS2 study shown a similar magnitude of reduction, or even simply a statistically significant reduction, this would seem more convincing. As it is, we may conclude that the final verdict on these specific fatty acid subclasses has not yet been rendered.

Despite these limitations and conflicting findings, it is not possible to dismiss these studies' results lightly. What, then, are clinicians and patients to make of them? It is clear that manipulation of dietary fats is not a "silver bullet" for reducing cardiovascular risk. Even if the risk reductions reported in these two studies were statistically significant, they would not be of the same magnitude reported for drug therapies or exercise.[9] It also seems unlikely that mid- to late-life changes in diet can undo the effects of eating habits sustained over many years. Although some observational data included in the meta-analysis covered as much as 23 years of follow-up, the lack of strong and consistent findings only further strengthens the case against a meaningful protective effect.

Yet it is surely unwise to abandon all recommendations about dietary fats. As in many areas of health and wellness, perhaps the best course is to encourage patients to form a balanced "portfolio" of risk reduction strategies — diet, exercise, drug therapy, and stress control, among others — at as young an age as possible. While we await the final word on dietary fats, a combined approach may provide a greater net benefit than the sum of its parts, and avoidance of overemphasis on any one element will help to prevent neglect of the others. ■

REFERENCES

1. McGill HC, et al. Origin of atherosclerosis in childhood and adolescence. *Am J Clin Nutr* 2000;72:1307s-1315s.
2. National Heart, Lung, and Blood Institute. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Full Report. 2012. http://www.nhlbi.nih.gov/guidelines/cvd_ped/peds_guidelines_full.pdf. Accessed May 30, 2014.
3. Daviglus ML, et al. Fish consumption and 30-year risk of fatal myocardial infarction. *N Engl J Med* 1997;365:1046-1053.
4. Hu FB, et al. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. *JAMA* 2002;287:1815-1821.
5. Ascherio A, et al. Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men. *N Engl J Med* 1995;332:977-982.
6. Albert CM, et al. Fish consumption and risk of sudden cardiac death. *JAMA* 1998;279:23-28.
7. Sugiyama T, et al. Different time trends of caloric and fat intake between statin users and nonusers among US adults: Gluttony in the time of statins? *JAMA Intern Med* Published online April 24, 2014. doi:10.1001/jamainternmed.2014.1927 [Epub ahead of print].
8. Wall R, et al. Fatty acids from fish: The anti-inflammatory potential of long-chain omega-3 fatty acids. *Nutr Rev* 2010;68:280-289.
9. Green DJ, et al. Exercise and cardiovascular risk reduction: Time to update the rationale for exercise? *J Appl Physiol* 2008;105:766-768.

MENOPAUSE

SHORT REPORT

Exercise for Symptoms of Menopause

By David Kiefer, MD

SOURCE: Sternfeld B, et al. Efficacy of exercise for menopausal symptoms: A randomized controlled trial. *Menopause* 2014;21:330-338.

The research presented in this article is part of a greater effort at five academic centers called MsFLASH (Menopause Strategies: Finding Lasting Answers for Symptoms and Health; msflash.org) in which menopausal women were randomized to yoga, exercise, or usual activity, and then further randomized to omega-3 fatty acid supplementation or placebo. Although the study is completed,

Summary Point

- Twelve weeks of aerobic exercise in previously sedentary women did not improve menopausal symptoms, but did modestly improve perceived sleep quality.

only the exercise arm has been published. In the current article, the analysis included 248 menopausal women who were randomized to an exercise regimen or usual activity for 12 weeks, and were assessed for the frequency and "bother" of vasomotor symptoms, sleep symptoms, and mood. The exercise protocol included three 40-60 minute, individualized, supervised aerobic trainings weekly, either on a treadmill, elliptical trainer, or stationary bicycle as per the study participant's choice. An intention-to-treat analysis was performed on the 106 exercise participants and the 142 women assigned to usual activity. Baseline characteristics between the two groups were similar, except for the fact that the exercise arm was older.

Both the exercise group and the usual activity group had a statistically similar decrease in hot flashes per day (2.4 and 2.6, respectively), although a sub-analysis by race found that white women had less hot flashes with exercise, whereas African American women had no benefit. The authors attribute this disparity to "racial differences in cardiovascular, metabolic, and neuroendocrine responses to exercise." There was a decrease in vasomotor symptoms "bother" in the exercise group, but it was not significantly different from the control group. Exercisers had better sleep, but only in perceived sleep quality, not insomnia symptoms, and had less depressive symptoms ($P = 0.028$; though significance was set at $P < 0.0125$, so this was not deemed significant). Health care providers may be faced with trying to help women with vasomotor symptoms negotiate the many possible treatment options. Although an intensive exercise regimen appears to only provide modest sleep benefits to women with menopausal symptoms as based on this methodologically sound study, the authors themselves point out that there are many other reasons to consider exercise for patients in this demographic. It should continue to be considered as part of an integrative treatment approach. ■

BACK PAIN

SHORT REPORT

Useful: Spinal Manipulation for Low Back Pain

By David Kiefer, MD

SOURCE: Bialosky JE, et al. Spinal manipulative therapy-specific changes in pain sensitivity in individuals with low back pain (NCT01168999). *J Pain* 2014;15:136-148.

This placebo-controlled trial of 110 people with low back pain of any duration was designed to elicit the contribution of the placebo effect to benefits ascribed to spinal manipulative therapy (SMT). In the case of this study, SMT was administered by physical therapists and consisted of a high-velocity, low-amplitude force applied to the pelvis to rotate the lower spine. In addition to a "no intervention" group, two placebo groups were established: 1) a placebo SMT intended to mimic true SMT but with different biomechanics, and 2) an enhanced placebo SMT, wherein they were told "The manual therapy technique you will receive has been shown to significantly reduce low back pain in some people." These groups all received their intervention six times over a 2-week period, with clinical outcomes (psychological questionnaires, mechanical pain sensitivity, thermal pain sensitivity, suprathreshold heat

Summary Point

- Spinal manipulative therapy provides benefits in one aspect of pain sensitivity for people suffering from low back pain.

response, and aftersensation) assessed at baseline and after the 2-week interventional period. In line with prior research, only the true SMT group showed a lessening of the suprathreshold heat response ($P \leq 0.05$), a rating of response to heat applied to the plantar aspect of the dominant foot, which was used in previous trials and thought to have particular relevance to clinical pain. Overall pain intensity and disability improved in all groups similarly over the 2-week time period. Elaborate statistical techniques utilizing chi-squared analyses and t-test between the numerous variables were used to compare the different groups, outcome measurements, and time points, in order to find differences/similarities. The authors conclude that the benefits of SMT are likely due to SMT itself, rather than expectations from SMT, and seem mostly to benefit the suprathreshold heat response rather than other measurements of pain sensitivity. Extrapolating from animal studies, the authors make a case for how SMT likely affects the dorsal horn of the spinal cord. Overall, these results seem to corroborate an effect of SMT that extends beyond simply a placebo response due to expectation and provider touch, as well as the need to attempt to further delineate populations (i.e., acute vs chronic low back pain) most amenable to this therapeutic approach. The bottom line? There is a tangible and physiologically plausible benefit for SMT for people with low back pain; it should be on clinicians' radar for this population. ■

EXERCISE

SHORT REPORT

An Herbal Adaptogen and Exercise

By David Kiefer, MD

SOURCE: Noreen EE, et al. The effects of an acute dose of *Rhodiola rosea* on endurance exercise performance. *J Strength Cond Res* 2013;27:839-847.

Most commonly used for general whole body support, insomnia, and anxiety, the herbal adaptogen, *Rhodiola rosea*, or roseroot, is also used to combat physical fatigue, the focus of this double-blind, crossover, placebo-controlled research study. Eighteen research participants were recruited from a college spinning class and given one 3 mg/kg dose of a *Rhodiola rosea* extract or placebo, and then analyzed for endurance exercise performance, mood, perceived exertion, and cognition. The *Rhodiola rosea* was in a powdered form and standardized for 3% rosavin and 1% salidroside, and dosed as per prior work on this topic. Statistically significant results were seen in the treatment group, including a faster 6-mile bike time trial (24 seconds faster, $P = 0.034$), slower heart rate during the warm up (4 beats per minute slower, $P = 0.0001$), and a lower rating of perceived exertion ($P = 0.04$), though other parameters including blood lactate and salivary cortisol and amylase, were equivalent statistically. The researchers compare these results to those of prior studies, corroborating physical benefits with one-time dosing of *Rhodiola rosea*, which the researchers and prior evidence tie to increases in endogenous opioid production. What is unclear, and not addressed by this study, is the effect of chronic *Rhodiola rosea* ingestion, which apparently may lose a positive effect in humans while it seems to function in this capacity in animals. Overall, these results are intriguing in that they point to short-term benefits, albeit Spartan and not necessarily clinically meaningful, for an herbal medicine otherwise thought of as a long-term adaptogen. ■

Summary Point

- One dose of *Rhodiola rosea* minimally, but statistically, improves endurance exercise.

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Scan the QR code to the right or log on to **www.cmecity.com** to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing each test, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME QUESTIONS

1. **Which of the following statements about oral probiotic supplementation is NOT true?**
   a. Probiotics are helpful in preventing and treating antibiotic-associated diarrhea.
   b. Most studies show that probiotics appear to be helpful for irritable bowel syndrome symptoms.
   c. Probiotics are a primary treatment for heart disease.
   d. Probiotics should be used with caution in patients who are immunocompromised.
2. **The omega-3 studies reviewed found a consistent, statistically significant cardioprotective effect with consumption of:**
   a. alpha-linolenic acid.
   b. Total omega-3 fatty acids
   c. Eicosapentaenoic acid and docosapentaenoic acid
   d. None of the above
3. **This study found benefits in exercise vs the control group in which of the following variables?**
   a. Hot flash frequency
   b. Hot flash "bother"
   c. Depression
   d. Perceived sleep quality
4. **The clinical outcomes analyzed in this study on spinal manipulative therapy include all of the following *except*:**
   a. suprathreshold heat response
   b. light touch excitability.
   c. thermal pain sensitivity.
   d. aftersensation.
5. **A recent study found that a 3 mg/kg dose of *Rhodiola rosea* extract improved:**
   a. mood.
   b. cognition.
   c. perceived exertion.
   d. sleep.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- present evidence-based clinical analyses of commonly used alternative therapies;
- make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and;
- describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

[IN FUTURE ISSUES]

Vitamin D and asthma

Mindfulness meditation and inflammation

Dietary supplement and prescription drug interactions

Dear *Integrative Medicine Alert* Subscriber:

Here's a change we know you'll like: From now on, you can earn continuing education credit for each individual issue.

No more having to wait until the end of a 6-month semester or calendar year to earn your continuing education credits or to get your credit letter.

Starting now, you can earn:

- 2.0 *AMA PRA Category 1 Credits*™ for each issue of *Integrative Medicine Alert* and up to 24 total annually.
- 2.0 American Osteopathic Association credits per issue and up to 24 annually

Here's how to do it:

1. Read and study the activity, using the provided references for further research.
2. Log on to cmecity.com to take a post-test. Tests can be taken for each issue or collectively at semester's end. First-time users must register on the site using the 8-digit subscriber number printed on your mailing label, invoice or renewal notice.
3. Pass the post-test with a score of 100%; you will be allowed to answer the questions as many times as needed to pass.
4. After completing the test, complete and submit an evaluation form.
5. Once the evaluation is received, a credit letter is emailed to you instantly.

If you have any questions about the process, please call us at (800) 688-2421, or outside the U.S. at (404) 262-5476. Our fax is (800) 284-3291 or outside the U.S. at (404) 262-5560. We are also available at customerservice@ahcmedia.com.

Thank you for your trust.

Sincerely,

Lee Landenberger
Continuing Education & Editorial Director