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INSIDE

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Glucosamine Sulfate for Osteoarthritis

By Dónal P. O'Mathúna, PhD

Dr. O'Mathúna is Senior Lecturer in Ethics, Decision-Making & Evidence, School of Nursing, Dublin City University, Ireland; he reports no financial relationship to this field of study.

GLUCOSAMINE SULFATE CONTINUES TO GROW IN POPULARITY AS A treatment for osteoarthritis. Global sales reached almost $2 billion in 2008, an increase of 60 percent over the previous five years.[1] This update will present the results of research published since this topic was last reviewed here two years ago. Further results from the NIH-funded Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) have since been published, along with some clinical guidelines.[2] Given glucosamine's widespread use, clinicians should be aware of recent research findings and their impact on osteoarthritis management.

Glucosamine occurs naturally in the body as one component of the cartilage and synovial fluid found within joints.[3] Glucosamine forms part of the structure of some compounds whose levels are reduced with osteoarthritis. A number of salts of glucosamine are available, with some debate over their relative effectiveness. While questions have been raised about the bioavailability of oral glucosamine, recent studies have shown that it is absorbed and can accumulate in synovial fluid.[3] However, its precise mechanism of action remains unclear, although a number of mechanisms have been proposed.

Background

Osteoarthritis is the most common form of arthritis and a leading cause of disability in the United States and Europe.[3] Prevalence increases with age, and is higher in women. However, actual values are difficult to estimate due to different diagnostic criteria and because about half the people with X-ray evidence of the disease report no symptoms.[4] The knees, hips, and small joints of the hands are most commonly affected, with pain and stiffness the most common symptoms.[3]

The etiology of osteoarthritis remains unclear. Once viewed as a consequence of aging, it is now known to develop due to complex

interactions involving genetics, age, gender, obesity, joint injury, and muscle weakness.[5] With the disease, cartilage inside joints gradually degenerates, exposing bone inside the joint and narrowing the joint space. This leads to stiffness and pain, and eventually the joint may become so immobile and painful that joint replacement surgery is the best alternative. (*See Figures 1 and 2.*) Osteoarthritis is only one of a number of arthritic diseases, resulting in the term arthritis being used commonly to refer to any pain and stiffness in the muscles and joints. For this reason, some who have osteoarthritis refer to it as arthritis. Technically speaking, arthritis involves inflammation in the joints and osteoarthritis is a non-inflammatory degenerative disease. All of the research reviewed here was conducted with older adults diagnosed with osteoarthritis.

Currently, osteoarthritis does not have a cure.[6] The Osteoarthritis Research Society International (OARSI) recommends that patients should be directed toward pharmacological and non-pharmacological treatments.[7] Conventional drugs for chronic pain, especially non-steroidal anti-inflammatory drugs (NSAIDs), are commonly used. However, long-term use of NSAIDs raises concerns about adverse effects, especially in combination with the other drugs many older people take.[2] Non-pharmacological modalities include education, lifestyle management such as exercise and weight reduction, and complementary therapies like acupuncture.[7]

Although all of these are important for managing symptoms, they do not treat the underlying pathology. Claims that dietary supplements can reverse cartilage damage, and that they have fewer adverse effects than pharmaceutical drugs, have fueled interest in complementary approaches to managing osteoarthritis symptoms. Several dietary supplements are being used for osteoarthritis.[8] Foremost among these are glucosamine and chondroitin, which are some of the most popular dietary supplements sold in the United States.[9] Although the two supplements are sometimes taken together, most studies have tested them separately.[5] This review will focus primarily on glucosamine sulfate.

Clinical Studies

Clinical studies have been conducted on glucosamine sulfate for osteoarthritis for more than 20 years. Many of the early studies were conducted in Europe using a product available by prescription in many European countries. These 1,500 mg sachets are to be dissolved in water and are manufactured by Rotta Pharmaceuticals of Italy. Studies with this product were sponsored by its manufacturer and generally had favorable results. Later independent studies tended to have negative results, raising concerns about bias. However, the differences among various trials are more complicated, involving different glucosamine formulations and study designs. Independent studies have used products available in the United States as dietary supplements, many of which are formulated as capsules, which may explain some of the differences with the Rotta product, which is dissolved before being taken.[4]

Over the last decade, a number of systematic reviews and meta-analyses have been published on glucosamine. These generally have been critical of the quality of earlier studies, finding they were small and of short duration. More recent meta-analyses have included only high-quality randomized controlled trials (RCTs). A Cochrane Collaboration systematic review, originally published in 2005, was updated in 2009.[10] The review now includes 25 trials with almost 5,000 osteoarthritis patients. Its conclusions remain unchanged from the original review. Overall, glucosamine was significantly better than placebo in producing a 22% reduction (from baseline) in pain, and an 11% improvement in function using the Lequesne Index (LI). However, significant differences were not found when outcomes were measured using the Western Ontario and McMaster Universities (WOMAC) osteoarthritis indices of pain, function, and stiffness. Studies comparing glucosamine to NSAIDs found similar benefits.

Sub-group analyses were performed to identify possible reasons for the variability between studies. The highest quality studies (having adequate allocation concealment) showed no benefit in pain and WOMAC scores, but were significantly better than placebo using the LI for a measure of function. Further differences were seen when studies with the Rotta product were compared to those us-

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Figures 1 and 2. A Healthy Joint and a Joint with Severe Osteoarthritis

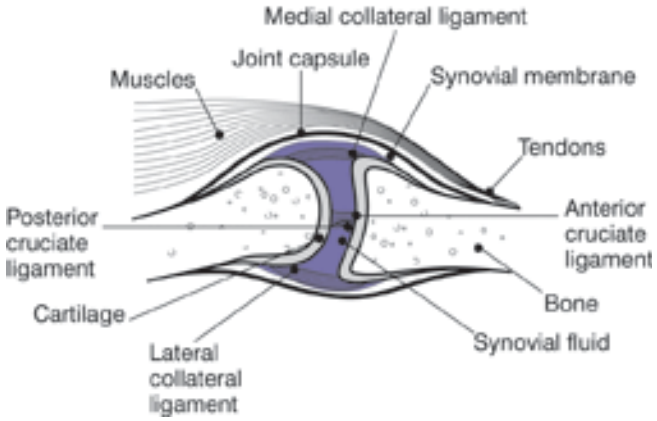

Figure 1. In a healthy joint, the ends of bones are encased in smooth cartilage. Together, they are protected by a joint capsule lined with a synovial membrane that produces synovial fluid. The capsule and fluid protect the cartilage, muscles, and connective tissues.

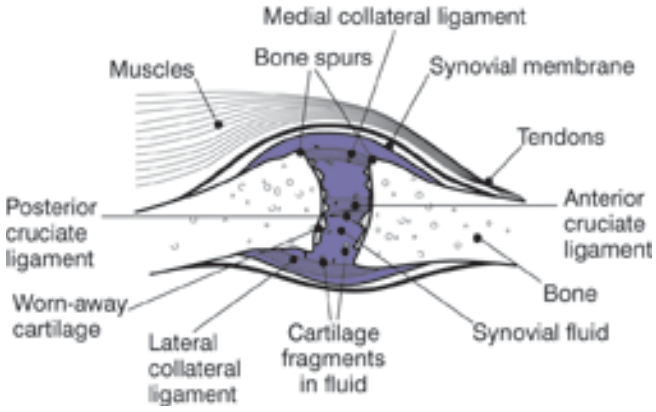

Figure 2. With osteoarthritis, the cartilage becomes worn away. Spurs grow out from the edge of the bone, and synovial fluid increases. Altogether, the joint feels stiff and sore.

Source: National Institute of Arthritis and Musculoskeletal and Skin Diseases. Handout on Health: Osteoarthritis. NIH Publication No. 10-4617. Available at: http://www.niams.nih.gov/Health_Info/Osteoarthritis/#pic_2. Accessed Jan. 15, 2011.

ing any other product. None of the latter produced significant improvements, while the Rotta product was significantly better than placebo for all pain measures, LI, and WOMAC indices. Two of these RCTs also measured joint space reduction within the knee by X-ray. Both studies found significant improvements for those using the Rotta product. Another review limited to RCTs lasting 1 year or longer similarly found good evidence of benefit using the Rotta product.[3] However, most of the Rotta studies were funded by the manufacturer and include some older ones of lower quality.

The most recent meta-analysis was published in 2010 and came to very different conclusions.[1] These reviewers limited their review to studies involving at least 200 patients. This was chosen as an indicator of methodological quality. They used a somewhat different method of analysis called a network meta-analysis, which uses more complex Bayesian statistical methods. Their review included 10 RCTs and concluded that "glucosamine, chondroitin, and their combination do not result in a relevant reduction of joint pain nor affect joint space narrowing compared with placebo."[1] This review since has been criticized for statistical methods and choice of various cut-off values for outcome measures.[11] These published letters were primarily from the authors of earlier systematic reviews and researchers at Rotta.

Meanwhile, findings from the NIH-funded GAIT trial continue to appear.[12] This study randomized more than 1,500 patients with symptomatic knee osteoarthritis to daily doses of either 1,500 mg glucosamine hydrochloride, 1,200 mg chondroitin sulfate, both glucosamine and chondroitin, 200 mg celecoxib, or placebo. Two-thirds of the participants were women. The primary outcome measure was a 20% reduction in knee pain measured by the WOMAC scale after six months of treatment. No significant reduction in pain occurred for the groups taking glucosamine or chondroitin, alone or together, compared to placebo, while pain was significantly reduced in the celecoxib group. Patients with moderate-to-severe joint damage as revealed by X-ray were asked to continue in a follow-up study focused on joint space width.[5] Patients continued to take the same treatment to which they had been assigned for a total of two years. No statistically significant differences in joint space width were observed between any of the groups.[2] The most recent publication examined pain and function in these participants who continued in the study for two years. No significant differences were found in WOMAC pain and function indices.

Adverse Effects

The GAIT study reported no significant differences in adverse effects between the groups, with a similar number of participants withdrawing from each group because of adverse events.[12] The follow-up study similarly reported no additional adverse effects in the glucosamine group.[2] Meta-analyses have found a similar safety profile between

placebo and glucosamine sulfate, with it comparing more favorably to NSAIDs.[10] Its safety profile is thus considered excellent.

Concerns have been raised that glucosamine might interfere with glycemic control in diabetic patients since animal models have demonstrated such effects. However, evidence from studies lasting up to 2 and 3 years have not substantiated these concerns.[2]

Glucosamine sulfate is obtained from chitin extracted from marine exoskeletons, which has raised concerns about allergic reactions. Those with seafood allergies probably should avoid glucosamine, depending on the severity of their allergy, or be carefully monitored if they try it.[6] Glucosamine also can be obtained from chitin in fungi, which may provide an alternative for people with a shellfish allergy.[3]

Conclusion

The GAIT study and a small number of others would appear to demonstrate than glucosamine hydrochloride is not effective in reducing pain or improving function for osteoarthritis patients. Only the Rotta brand of glucosamine sulfate has consistently demonstrated effectiveness in reducing symptoms and slowing joint deterioration. However, as the most recent meta-analysis demonstrates, when only the largest and highest-quality RCTs are included, even those benefits fade, although this meta-analysis may have been overly restrictive in how it measured effectiveness.

Product quality has been shown to be problematic with glucosamine dietary supplements available in the United States. One study found that products contained between 0%–115% of the mg stated on the label, while another contained between 59%–138% of labeled sulfate.[13] This may explain some of the lack of efficacy found with non-Rotta products.

Recommendation

For those with osteoarthritis, a trial of glucosamine sulfate may be warranted, especially when they do not respond well to conventional treatments. Symptoms should be evaluated carefully over a few months. However, even in those trials where glucosamine sulfate has been found to be effective, participants continued to use other analgesics when pain or discomfort were particularly problematic. In addition, the vast majority of trials have been conducted with knee osteoarthritis. Glucosamine sulfate may not be effective with osteoarthritis in other sites, as was recently found in a RCT of patients with degenerative lumbar osteoarthritis.[14] As with many chronic conditions, control of weight, exercise, and other symptom-relieving strategies will remain important in the overall management of osteoarthritis. ■

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Now How Much Vitamin D and Calcium Should We Take?

ABSTRACT & COMMENTARY

By David Kiefer, MD

Dr. Kiefer is Clinical Instructor, Family Medicine, University of Washington, Seattle; Clinical Assistant Professor of Medicine, University of Arizona, Tuscon; Adjunct Faculty, Bastyr University, Seattle; he reports no financial relationships to this field of study.

Source: Ross AC, et al. The 2011 Report on Dietary Reference Intakes for Calcium and Vitamin D from the Institute of Medicine: What Clinicians Need to Know. *J Clin Endocrinol Metab* 2011;96:53-58.

Synopsis: *An evaluation of medical research by the IOM establishes new RDAs for vitamin D (600-800 IU) and calcium (700-1300 milligrams).*

The year 2010 ends with a re-visitation of two "hot" supplements, calcium and vitamin D, this time by the venerable Institute of Medicine (IOM). The IOM committee assigned to this task consisted of 14 scientists who met eight times, collecting input also from public meetings and from "stakeholders" via the internet. The committee conducted a literature review to augment two recent reviews (2007 and 2009) on calcium and vitamin D by the Agency for Healthcare Research and Quality. The committee reviewed evidence of both the skeletal and "extraskeletal" effects of these two nutrients, updating its recommendations from the prior 1997 report. Overall, they were convinced of a cause-effect connection between both vitamin D and calcium and bone health, leading them to establish Recommended Daily Allowances (RDA) for calcium of 700-1,300 milligrams daily and vitamin D of 600-800 International Units (IU) daily (*see Table 1*). These values are different for some of the age groups compared to the 1997 analysis. The IOM was less impressed by the data for non-bone related conditions, and did not factor that evidence into the dosage ranges listed.

There are several characteristics of the IOM approach that will help to understand these recommendations and put them into context with other research results. First of all, a very important part of this analysis is that it was done in the context of the average "normal" person, that is, for people who don't have specific disease states. In addition, the vitamin D intake recommendations were set assuming little to no sun exposure, aiming to help 97.5% of the population (the definition of RDA) achieve a serum 25-hydroxyvitamin D (25(OH)D) of 20 ng/mL. The sun exposure variable was removed to avoid the unknowns regarding the effects of sunblock use, latitude, skin pigmentation, genetic factors, and extent of outdoor activity.

The IOM called the evidence inconsistent, inconclusive to causality, and insufficient to serve for establishment of dosages for cardiovascular disease, cancer, diabetes, falls, autoimmune disorders, and other chronic diseases. The IOM found some "U-shaped" effects for vitamin D, meaning that there might be increased risk at low and high dose ranges, and the lowest risk in moderate dose range for some medical conditions (all-cause mortality, cardiovascular disease, some cancers, falls, and fractures), leading to continued use of the Upper Limit (UL) values above which increased risk of adverse effects may exist. The actual 2011 UL values are different than in 1997; calcium's had been 2,500 milligrams daily, and is now 1,000-3,000 milligrams daily, depending on age, and the vitamin D UL increased from 2,000 IU to 4,000 IU for most age groups. The vitamin D UL was set lower than the 10,000 IU limit of toxicity due to possible adverse effects with longer term chronic administration (as opposed to acute toxicity) and the committee's stated concerns about serum 25(OH)D levels above 50 ng/mL.

The IOM pointed out the need for further research, especially in the area of laboratory parameters to establish safe high and low ranges, and concluded that the well-publicized "epidemic" of hypovitaminosis D was overestimated.

Although the IOM committee commented on serum 25(OH)D levels, it also stated that an in-depth review of this topic was beyond the scope of the report. As much as it recognized that 25(OH)D levels do represent vitamin D intake and sun exposure, the committee was less impressed by the evidence for 25(OH)D levels and connection to certain disease states, or lack of same. The committee states that 25(OH)D of 20 ng/mL covers the requirements of 97.5% of the population, and that the effects of chronically high serum levels (for example, 50 ng/mL) remain unproven, mandating a certain "margin of safety for public health."

Putting the recommendations in the context of dietary intake, the committee referred to nutritional research finding that most of the population meets basic calcium needs and vitamin D intake requirements to reach serum 25(OH)D of 20 ng/mL. The notable exceptions are girls aged 9-18 years because of their high calcium intake needs, and people with poor nutrition, in institutions, or those with dark skin pigmentation who might not reach sufficient serum vitamin D levels.

COMMENTARY

When the IOM report was released, it sent waves of

Table 1: IOM RDA for Calcium (mg) and Vitamin D (IU) using bone health as an indicator, 1997 vs. 2010 (Changes in Bold)

Ages	Calcium, 1997*	Calcium, 2010	Vitamin D, 1997*	Vitamin D, 2010
1-3	500	**700**	200	**600**
4-8	800	**1000**	200	**600**
9-13	1300	1300	200	**600**
14-18	1300	1300	200	**600**
19-30	1000	1000	200	**600**
31-50	1000	1000	200	**600**
51-70	1200	**1000** (men), 1200 (women)	400	**600**
71+	1200	1200	600	**800**

*The quality of the data available in 1997 was considered only adequate to establish Adequate Intakes (AI) rather than the more rigorous RDA; the numbers listed for 1997, therefore, are AI values.

Source: Ross AC, et al. The 2011 Report on Dietary Reference Intakes for Calcium and Vitamin D from the Institute of Medicine: What Clinicians Need to Know. *J Clin Endocrinol* Metab 2011;96:53-58.

disbelief among many clinicians and researchers, especially due to the very conservative vitamin D dosing recommendations. Their serum 25(OH)D of 20 ng/mL cutoff for adequacy seems woefully low. Many studies on falls or fractures failed to find a benefit below 25-30 ng/mL,[2] and some preliminary data on vitamin D and treatment of upper respiratory infections found thresholds of 30 ng/mL, above which there was benefit and below which no effect. Also, while serum 25(OH)D < 20 ng/mL is recognized as vitamin D deficiency, some data are accumulating that 20-29 ng/mL may be a relative vitamin D insufficiency, making 30 ng/mL and above close to optimal[1]; this would all make the IOM target less than ideal. With respect to vitamin D dosing, 600-800 IU seems very low, especially given that most experts are recommending 800-1,000 IU daily at the minimum for maintenance, with higher doses in high-risk groups or to correct vitamin D deficiency or insufficiency.[1,2]

The IOM report also seemed to overstate the vitamin D safety concerns. One expert continues to postulate the safety of 10,000 IU vitamin D daily, and the problems with vitamin D use in people with granulomatous disorders and lymphomas when serum 25(OH)D rises above 30 ng/mL could be avoided simply with lower (400 IU) daily vitamin D dosing in those groups without applying such conservative dosing recommendations to the population as a whole.[1]

In addition, there are issues regarding how applicable these recommendations are to real clinical situations involving real patients. Excluding the involvement of sun is probably an important research approach, but one that baffles physicians actually treating patients, few of whom would fall into such a limited category. In addition, the IOM focused on "normal" patients, or ones without relevant medical conditions. This is in contrast to many of the published research trials examining calcium, vitamin D, or both for the treatment or prevention of various diseases in specific populations. Therefore, the IOM recommendations may simply be different from other results in the medical literature for this reason.

With respect to calcium, the new IOM recommendations are mostly unchanged from the 1997 levels, with only three modifications (*See Table 1*). Compared to other expert groups and reviews, such as the NIH Consensus Statement from 1994, the new recommendations remain lower.[3] Are these new doses still too low? Is this conservative approach warranted due to some of the known adverse effects with calcium intake? The medical literature continues to evolve in its pursuit of answers to these questions. For example, it is unclear whether the IOM Committee addressed recent concerns, albeit controversial, over the possible extra risk of cardiovascular events with calcium supplementation,[4] or the possible connection with prostate cancer risk, as previously addressed in *Alternative Medicine Alert*.[5] On the flip side, the positive effects of calcium supplementation on prevention of bone loss and osteoporosis occur in the range of 1,000-1,200 milligrams daily,[6] and are adequately covered

in the 2011 IOM report.

Overall, the IOM committee members failed to jump on the vitamin D bandwagon in its 2011 reassessment, setting a low-bar public health interventional strategy, and leaving physicians and patients alike without the official "OK" in repletion attempts. Closely paying attention to upcoming research trials will probably be the better course of action for clinical guidance. Calcium, in its own rite, is a mineral with a complicated history, still evolving in some respects (i.e., recent cardiovascular risks) but mostly unchanged in this current report; most health care practitioners continue to recommend calcium supplementation up to but not exceeding RDA levels for women in all age groups, paying particular attention to calcium dosing in girls ages 9-18. ■

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Symptoms and Asymptote: Echinacea and Colds

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *The results of this well-done study suggest that a specific formulation of echinacea may offer modest benefit to people with the common cold, but that such benefit is statistically, and likely clinically, insignificant. Data from the trial relating to physician-patient interaction and clinical response have yet to be published.*

Source: Barrett B, et al. Echinacea for treating the common cold. *Ann Intern Med* 2010;153:769-777.

A respectable collection of research data exists regarding the effectiveness of echinacea against the common cold, yet a definitive recommendation remains elusive. Published results and conclusions vary widely, as do the methodologies employed. In part as an effort to remedy this situation, in part to further explore the therapeutic implications of the doctor–patient relationship, the authors of this study designed a 2-way factorial study in which subjects were randomized to 1) receive no, standard, or enhanced clinical interaction in one direction (33% chance), and 2) to receive no pills, placebo (blinded), echinacea (blinded), or open-label echinacea (unblinded) in the other direction (25% chance).

Subjects were recruited through advertisements and community events, and subsequently underwent screening via telephone interview. Subjects had to be 12 years of age or older with cold symptoms having developed within 36 hours. People with a history of allergic rhinitis and typical allergic symptoms, as well as those using antibiotics or decongestants, were excluded.

Each subject was assigned an envelope-within-an-envelope—this permitted group assignment to be revealed immediately after consent was obtained. A research assistant opened the larger envelope for group assignment and subjects then received and took their first dose of pills. The alkylamide-rich echinacea supplied to subjects contained the equivalent of 675 mg of *E. purpurea* root and 600 mg of *E. angustofolia* root, each standardized to 2.1 mg of alkylamides. Placebo pills were identical in appearance and similar pill bottles were used. Subjects received 2 tablets at enrollment, followed by 2-tablet doses 3 more times within 24 hours, and then 1 tablet 4 times a day for the next 4 days. Phytochemical analysis of the echinacea product was completed by an independent source at various times throughout the study and revealed stable constituent concentrations.

For the two-thirds of subjects who would be seeing a clinician, a second, smaller envelope was opened by the study clinician. This second envelope described allocation to standard or enhanced medical visit.

Symptoms were to be self-rated twice daily until they resolved, up to a maximum of 14 days. Nasal washings were collected at enrollment and 2 days later. These were analyzed for interleukin-8 levels and neutrophil counts.

The primary outcome of interest was the area under the curve for global symptom severity, with duration and severity assessed twice daily by self-report. Secondary outcomes of interest focused on measures of psychological and immunological impact. Tools employed included the Wisconsin Upper Respiratory Symptom Survey (short version), the Medical Outcomes Study Short Form-8 Scale, the Euro-Qol's feeling thermometer, the 4-item Cohen Perceived Stress Scale, the Ryff Personal Rela-

tionships Scale and the Life Orientation Test.

At trial's end, the average area under the curve for global severity and illness duration were lower in the blinded and open-label echinacea groups than in either the blinded placebo or no-pill groups. Mean global severity was 236, 258, 264, and 286 for the blinded echinacea group, the unblinded echinacea group, the blinded placebo group, and the no-pill group, respectively. Mean illness duration in the blinded and unblinded echinacea groups was 6.34 and 6.76 days, respectively, in comparison to 6.87 days in the blinded placebo group and 7.03 days in the no-pill group. An efficacy analysis that compared duration of illness in the two blinded groups (echinacea and placebo) yielded a mean difference of 0.53 day (Confidence Interval [CI], -1.25 to 0.19 days) and a T of 1.97 ($P = 0.075$). Subgroup analysis of 351 people identified with very early symptom onset revealed insignificantly reduced illness duration and global severity in those receiving echinacea compared with the no-pill or blinded placebo groups. No statistically significant differences were identified between the groups for secondary outcomes of interest. Incidence of adverse events was similar across all four groups.

The authors concluded that the pharmacologic activity of echinacea likely provides at best a modest benefit for people with the common cold.

■ COMMENTARY

Viral respiratory infections are a major reason for missing school and work, and the study authors point out that billions of dollars are lost as a result, not to mention the dollars expended through doctor's visits. So it makes sense that investigation into safe means of preventing and treating upper respiratory infections needs to be supported. But perhaps only to a point, and with respect to echinacea it feels, at least to this reviewer, as though we may have reached that point.

These researchers are to be praised for their efforts—they developed and carried out a well-done trial, with additional results yet to be reported that promise to be compelling. There are shortcomings to make note of, including the perspective many hold that tincture of echinacea is more effective than pills. The authors themselves make clear that the results of but one of a wide variety of echinacea formulations being put to the test cannot rationally be used to judge the effectiveness of all such potential formulations. The authors also readily report that their trial may have been underpowered. The question of generalizability is legitimate if for no other reason than that the population in question is clearly unusual—out of the initial > 3,000 people screened for participation a total of 914 were already enrolled in another clinical study. In addition, retention was unusually high with approximately 98% of intended data collected, the largest data gap being for the nasal wash, where 33 subjects did not return within 24-72 hours after the first wash. Still, the results are meaningful and have clinical relevance—though the effect of echinacea in this setting was mild-to-moderate at best and did not achieve statistical significance, a half-day quicker to feeling better counts for something in the minds of some.

The authors point out that literally hundreds of studies examining the effectiveness of echinacea against the common cold have been published, including randomized trials. The array of results run the gamut from echinacea being dramatically effective, to its activity being equivalent in nature to placebo, and seemingly everything in between. Results of the current trial suggest that the specific formulation of echinacea studied may offer some benefit in the setting of an acute cold, but that the effects are statistically and, for many, clinically insignificant.

It may be that we are nearing the place of diminishing returns from this line of investigation. Though upper respiratory infection is a costly plague of mankind it is, nonetheless, a generally self-limited malady that many studies suggest might be avoided through general lifestyle measures such as getting adequate sleep; washing one's hands frequently; avoidance of touching the eyes, nose and mouth; managing stress in healthy ways; holding to a healthy diet and exercise regimen; and staying socially engaged even during cold season.

Beyond our moms' traditional advice, almost all cold remedies fail in providing their purported health benefits, yet some studies of specific formulations of echinacea suggest a potentially meaningful shortening of duration and lessening of severity of illness, and with a wide safety margin. Perhaps as medicine further embraces the individual nature of patients and their response to treatment, practitioners can find comfort in both the published science and the clinical experience that some people with upper respiratory infections do better with echinacea, some do not, but the remedy appears to be safe so it's worth a try.

The lines for treatment and symptom relief, though often approaching one another, do not always make for a clean and consistent intersection. In select clinical circumstances, such as the use of echinacea for the common cold, it's time to get comfortable with inconsistency. ■

An Honest Response—Placebos and IBS

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *Findings of this ground-breaking randomized controlled trial suggest that patients with irritable bowel syndrome who receive treatment with placebo tablets, and who are fully aware that they are taking a placebo, have significantly greater relief of symptoms compared with patients who receive no treatment at all. Accessing the placebo effect may not require deception at all.*

Source: Kaptchuk TJ, et al: Placebos without deception: A randomized controlled trial in irritable bowel syndrome. *PLoS ONE* 2010;5:e15591.

The authors of this randomized, controlled, single center study sought to assess the feasibility of recruiting people with irritable bowel syndrome (IBS) to participate in a trial of open-label placebo, and to evaluate whether an open-label placebo pill combined with a persuasive rationale would be more effective than no-treatment in relieving IBS symptoms over the course of 3 weeks' time.

Participants were recruited from advertisements for "a novel mind-body management study of IBS" in newspapers and fliers, and from health care provider referrals. Subjects had to be older than age 18 years, meet Rome III criteria for IBS, and have a score ≥ 150 on the IBS Symptom Severity Scale (IBS-SSS). They were permitted to continue any IBS medications they were taking provided they had been on stable doses for at least 30 days prior to enrollment, and were asked not to make significant medication or lifestyle changes during the trial period.

Participants were randomized into two groups: 1) open-label placebo pill twice daily, or 2) no-treatment. Prior to randomization, patients from both groups met with either a physician (male) or nurse practitioner (female), based solely on practitioner availability, and were asked what they had heard of the "placebo effect." The provider then explained in clear terms that a placebo pill is an inactive substance like a sugar pill containing no medication. This was followed by the reading of a script, lasting approximately 15 minutes, that described the following "four discussion points:" 1) the placebo effect is powerful; 2) the body can automatically respond to taking placebo pills like Pavlov's dogs who salivated when they heard a bell; 3) a positive attitude helps but is not necessary; and 4) taking the pills faithfully is critical. Additionally, participants were told that "placebo pills…have been shown in rigorous clinical testing to produce significant mind-body self-healing processes."

Subjects were told that one-half of them would be receiving an open-label placebo while the other half would receive no treatment, but that each group was critical to the trial. They were also told that each of them would receive management recommendations for IBS symptoms at the end of the trial. The supportive patient-provider relationship and contact time were similar for both groups.

It was at this point, during the last moments of the interview, that subjects were told of their allocation status; those randomized to the open-label placebo group were given a typical prescription medicine bottle that contained blue and maroon gelatin capsule placebo pills, with the label clearly marked "placebo pills—take 2 pills daily." Patients in the no-treatment arm were reminded again of their important role in the trial.

Assessment questionnaires were completed during study visits with the assistance of a blinded assessor at baseline, midpoint (day 11), and completion (day 21). All visits took place in the context of a warm, supportive patient–practitioner relationship. Subjects receiving placebos were given a short reminder about the "four discussion points" after a brief examination during the midpoint visit, while those in the no-treatment arm were encouraged and thanked for their important contributions to the research.

The primary outcome of interest was the result of the IBS Global Improvement Scale (IBS-GIS). Other measures included the IBS-SSS, the IBS-Adequate Relief (IBS-AR), the IBS Quality of Life (IBS-QoL), side effects, and pill counts. At trial's end, subjects were given a short qualitative open-ended check-out questionnaire and asked for written responses, with unique questions posed to each of the two groups (results to be reported elsewhere). Intention-to-treat analysis was employed.

A total of 92 potential subjects were screened and 80 (70% female) were ultimately randomized into the two groups (n = 43 in the no-treatment arm). Participants in the open-label placebo group had significantly better scores on the main outcome measure, the IBS-GIS, at both the midpoint and endpoint measures (5.2 ± 1.0 vs. 4.0 ± 1.1, $P < 0.001$ and 5.0 ± 1.5 vs. 3.9 ± 1.3, $P = 0.002$, respectively). Statistically significant differences favoring placebo were identified at both time points for reduction in symptom severity (IBS-SSS) and adequate relief (IBS-AR), and a trend toward significance at the endpoint on improvement in quality of life (IBS-QoL) was noted. No significant differences on any outcome measure were found based on which practitioner (male physician or female nurse practitioner) met with the participants. Based on the responses to qualitative questions, it appeared that subjects understood they were taking a placebo and were not overly disappointed if assigned to the no-treatment group.

The authors conclude that placebos administered without deception in the context of a supportive patient–practitioner relationship and plausible rationale may be an effective treatment for IBS.

■ **COMMENTARY**

This study is flat out awesome. It is the first randomized controlled trial to compare an open-label placebo to a no-treatment control, and the results suggest strongly that placebo effects reflecting symptomatic improvements can be accessed without deception. To review, subjects who received the open-label placebo had almost twice the improvement in IBS symptoms experienced by the no-treatment group.

Most practitioners share the belief that beneficial responses to placebo treatment require concealment or deception, and thus raise an ethical dilemma. And yet, as the authors point out, a not insignificant proportion of physicians report having prescribed medications they believe to have no specific effect on a patient's condition. Based on the current study's results, however, perhaps placebos can be offered to patients with promise of benefit, if used in the same context and with positive framing, for any of a variety of disorders whose primarily clinical manifestations are subjective.

The authors note that the diagnosis of IBS, a chronic functional gastrointestinal disorder characterized by abdominal pain and discomfort associated with altered bowel habits, is one of the top 10 reasons for seeking primary care, and that few effective therapies have been identified. They also reference previous research that showed placebo responses in IBS are substantial and clinically significant.

There are methodological challenges to be acknowledged—the means of attracting participation may have biased the sample toward people more open to mind-body therapies; the sample size is relatively small and the study's duration quite short; in light of these latter facts the significant amount of missing data is concerning. Still, the findings are stunning. It seems that practitioners might ethically be able to use the placebo effect to utmost advantage in helping patients with select maladies while still treating them with respect and honesty, all the while continuing to merit their full trust. It seems an "open-label placebo" is no longer an oxymoron. ■

Should Everyone Be on Fish Oils?

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Dr. Karpman is Clinical Professor of Medicine, UCLA School of Medicine. Dr. Karpman reports no financial relationship to this field of study. This article originally appeared in the November 29, 2010 issue of Internal Medicine Alert. *At that time it was reviewed by Gerald Roberts, MD, Assistant Professor of Medicine, Albert Einstein College of Medicine, New York, NY. Dr. Roberts reports no financial relationships to this field of study.*

Synopsis: *Marine n-3 PUFAs act as pleiotropic agents on the cardiovascular system with a diverse range of effects most of which are beneficial for patients with known cardiovascular disease and possibly, they may even have beneficial effects with regard to the primary prevention of cardiovascular disease.*

Source: Saravanan P, et al. Cardiovascular effects of marine omega-3 fatty acids. *Lancet* 2010;376:540-550.

THE MARINE OMEGA-3 POLYUNSATURATED FATTY ACIDS (n-3 PUFAs) eicosapentaenoic acid and docosahexaenoic acid are present mainly in all the fish and commercially available supplements that are available either over the counter as fish oils or as concentrated pharmaceutical preparations. Fish oil supplements have been becoming increasingly popular because several health benefits have been attributed to them in both the medical and lay literature. Substantial benefits have been reported in relation to diseases of the cardiovascular system and, in fact, published medical guidelines recommend use of these agents in some cardiac disorders.[1,2] Although much research had been focused on this area during the past three decades, such basic issues as the appropriate doses needed to achieve beneficial reduction in cardiovascular events are still unclear.

■ **COMMENTARY**

Numerous prospective epidemiological studies have reported that high fish consumption was associated with a lowered mortality from coronary artery heart disease,[3-6] and this hypothesis has been supported by findings of the landmark DART study,[7] a randomized secondary prevention trial concerned with long-term dietary intervention in men who had suffered myocardial infarctions (MI). A 30% reduction in total mortality and morbidity related to coronary artery heart disease (CAD) was reported in patients who were randomly assigned to consumption of fatty fish twice weekly. Another large intervention trial of secondary prevention after MI demonstrated a substantial reduction in all-cause and cardio-vascular mortality in patients who were treated with only 1 g per day of n-3 PUFA supplementation.[8] Data on the effects of these agents on the risk of development of CAD in healthy participants are inconsistent; however, the available evidence in primary prevention of CAD suggests that those patients with hyperlipidemia and/or diabetes might benefit the most by using fish oil. The main benefit reported for secondary prevention relates to the reduction in occurrence of sudden cardiac death, especially in patients with previous

MI.[9] Much research has been devoted to the antiarrhythmic effects of these agents and it has been suggested that the conflicting findings may be attributable to differences in the mechanisms of arrhythmia initiation in subsets within the study populations. Finally, it must be noted that no significant reduction in sudden cardiac death or CAD events was reported in a cohort of patients who had received optimal use of conventional therapy such as beta blockers, statins, and angiotensin converting enzyme inhibitors and even in patients who had a high rate of revascularization procedures performed,[10] suggesting that n-3 PUFA therapy may be of no additional value in patients who already are receiving maximum medical therapy for their cardiac condition.

The risk of heart failure appears to be inversely related to fish consumption and, in a large study with 60,000 participants who were followed for up to 13 years, there was a reduction in deaths attributable to heart failure in those participants who reported an increase in fish intake.[11,12] Thus far, no significant data are available regarding the effect of n-3 PUFA on the prevention or reduction of stroke in symptomatic or asymptomatic patients with or without atherosclerotic carotid arterial disease. A consistent effect of these agents is their ability to lower plasma triglyceride concentrations by reducing the hepatic synthesis of triglycerides and by increasing clearance of circulating triglycerides.[13] Because prior studies have demonstrated significant benefit in the reduction of cardiovascular events in patients with type 2 diabetes, large prospective studies assessing the role of n-3 PUFA intake on risk reduction for cardiovascular events are underway.[14]

It has been suggested that the dietary intake of fish is the most desirable way to increase the n-3 PUFA intake, but it must be recognized that 1 g per day of the supplement is equivalent to the fish oil present in about 55-85 g of fresh tuna, sardines, salmon, or trout and in 652 g of Atlantic cod fish. These high intakes of fish are extremely difficult to achieve in most parts of the world; therefore, an argument can be made for prescribing supplements to all patients

CME Instructions

Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

CME Objectives

After completing the program, physicians will be able to:

a. present evidence-based clinical analyses of commonly used alternative therapies;
b. make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
c. 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.

CME Questions

5. The form of glucosamine with the best evidence for effectiveness in osteoarthritis is:
a. glucosamine hydrochloride.
b. glucosamine dioxide.
c. glucosamine sulfate.
d. glucosamine sulfoxide.

6. Glucosamine is believed to benefit osteoarthritis patients because it is a natural component of:
a. bone.
b. cartilage.
c. muscle.
d. skin.

7. Adverse effects observed with glucosamine have been found to be similar to those with:
a. placebo.
b. NSAID.
c. digoxin.
d. All of the above

8. The joint American College of Cardiology and American Heart Association statement on n-3 PUFA use in patients with coronary artery disease recommends:
a. an intake of at least two fish meals per week.
b. an intake of one fish meal per week with 1 g per day of n-3 PUFA ethyl esters.
c. supplemental therapy for 1 year of 4 g per day of n-3 PUFA ethyl esters for those who have suffered a myocardial infarction.
d. four fish meals per week for primary prevention of symptomatic coronary artery heart disease.

Answers: 5. c, 6. b, 7. a, , 8. a.

for whom reliable increases in n-3 PUFA are indicated.[15] Finally, it should be noted that the joint American College of Cardiology and American Heart Association guidelines statement on the use of n-3 PUFA currently recommends an intake of at least two fish meals per week in patients with known CAD and supplemental therapy for 1 year with 1 g per day of a combination of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) for those patients who have had a prior myocardial infarction.[1] The evidence for these recommendations have been lent support by the results of many observational studies, although the recommendation for treatment of patients post MI were derived from only one study;[8] therefore, further large-scale investigations are needed in this patient group as well as in the overall area of primary prevention.

In conclusion, marine n-3 PUFAs act as pleiotropic agents on the cardiovascular system and appear to be associated with beneficial anti-inflammatory, anti-atherosclerotic, anti-immunomodulatory, and anti-arrhythmic effects. However, assessment of the effectiveness of these agents in the setting of optimum conventional drug therapy and elucidation of the mechanisms of action of the perceived benefits needs to be established on a larger scale in carefully controlled, double-blind trials and with issues of sustainable fishing practices at the forefront. ■

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