



EDUCATIONAL OBJECTIVE: Readers will understand that the treatment of osteoarthritis differs depending on the patient's clinical presentation

ROLAND W. MOSKOWITZ, MD, MS (MED)*

Clinical Professor of Medicine, University Hospitals,
Case Medical Center, Cleveland, OH

The 2012 ACR guidelines for osteoarthritis: Not a cookbook

"When I see a patient with arthritis coming in the front door, I leave by the back door."

—Sir William Osler

FORTUNATELY for today's physicians treating patients with osteoarthritis, we need not be as pessimistic as Osler was more than a century ago when he uttered his now-famous words. Still, there is no magic bullet for the contemporary clinician treating an elderly patient with osteoarthritis. Instead, there are many imperfect bullets, and choosing between them is always a balancing act between benefit and risk from various agents: nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics such as acetaminophen and tramadol, opioids, and supplements such as glucosamine and chondroitin sulfate.

So there was great interest when, in 2012,¹ the American College of Rheumatology (ACR) updated its previous guidelines (from 2000) on drug and nondrug therapies for osteoarthritis of the hip and the knee² and added new recommendations on osteoarthritis of the hand.

Revising the guidelines was appropriate, since new therapies have become available. But, as the guideline authors state, with osteoarthritis, as with other diseases, guidelines cannot be a "cookbook."

The treatment approach differs depending on the patient's clinical presentation and on the preferences of the patient and the physician. Often, more than one approach is possible, and more than one approach may be

appropriate in a given patient at a given time. The guideline authors also point out that some physicians may disagree with some of the recommendations.

I wish to review here several of the key recommendations. But I also provide some of my personal perspective and experience after 4 decades of treating patients with osteoarthritis.

■ HOW THE GUIDELINES WERE MADE

The new ACR guidelines were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, a formal process to develop recommendations that are as evidence-based as possible.³

The authors are outstanding experts in the field of osteoarthritis from throughout the United States and Canada. Further, the recommendations were voted on by a "technical expert panel" representing the fields of rheumatology, orthopedics, physical medicine, and rehabilitation, from both academic medicine and private practice. This representation provides a balance of input from the types of clinicians frequently involved in managing osteoarthritis.

The initial literature searches for drug therapies were conducted during late 2008, and those for nonpharmacologic treatments were conducted during the second and third quarters of 2009. The goal of the literature searches was to identify the most current systematic reviews and meta-analyses that would provide reliable estimates of benefits of intervention for the prespecified clinically relevant outcomes of pain and function, as well as data on safety.

The authors point out that some physicians may disagree with some of the recommendations

*The author has disclosed that he has served as a consultant for Eli Lilly, Johnson and Johnson, Pfizer, and Purdue Pharma and as a member of an advisory committee or review panel for Schiff Nutrition.

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Recommendations:**For or against, strong or weak—
and the informed patient's perspective**

Therapies received the following possible recommendations:

- Strong recommendation to use
- Weak (or conditional) recommendation to use
- No recommendation
- Weak (or conditional) recommendation not to use
- Strong recommendation not to use.

A strong recommendation required high-quality evidence and evidence of a large difference between desirable and undesirable effects of the treatment. A conditional recommendation was based on the absence of high-quality evidence, evidence of only a small difference between desirable and undesirable effects of the treatment, or both.

One interesting feature of these recommendations is that they took into account how informed patients might themselves evaluate the data with their medical condition.

For instance, if a therapy received a strong favorable recommendation, we can assume that most informed patients would choose to receive it, and we can shape our interaction with the patient accordingly. A conditional recommendation means that most informed patients would choose the treatment—but many would not, and physicians should keep the patient's values and preferences in mind.

I admit I had a problem with the meaning of the word “conditional” in the context of these guidelines. When evaluating a treatment, the term “weak” is readily understood and clearer. By using the word “weak,” one is making a positive statement in support of use but letting you know that the data and recommendation are weak. The word “conditional” is less readily defined and does not necessarily imply support for use.

Recommendations were drafted after discussion of the evidence at each meeting of the technical expert panel. Consensus was defined as 75% or more of the members of the panel voting to either strongly or conditionally recommend using a therapy, to either strongly or conditionally recommend not using it, or to choose not to make a recommendation on its use.

■ OSTEOARTHRITIS OF THE HAND: NO STRONG RECOMMENDATIONS

The technical expert panel gave no strong recommendations for any nondrug or drug treatment for osteoarthritis of the hand.

Conditional recommendations for nondrug treatments

The panel conditionally recommended the following:

- All patients with osteoarthritis of the hand should be evaluated either by their primary physician or by an occupational or physical therapist, particularly with respect to ability to perform activities of daily living.
- Assistive devices such as jar openers, key turners, and pull tabs for zippers should be recommended, as needed.
- Patients should be instructed in joint protection and in the use of thermal treatments (eg, heating pads, ultrasound devices, hot packs, and ice packs).

Comments. Appliances are often beneficial in patients who have involvement of the first carpometacarpal (trapeziometacarpal) joint. Although over-the-counter thumb splints are an option, referral to an occupational therapist for splint prescription is advantageous to achieve a comfortable fit and, importantly, for instructions to the patient on how to avoid joint trauma.

It would be unrealistic to expect primary care physicians and internists to have the expertise to make detailed recommendations about orthopedic appliances. Accordingly, referral to an occupational therapist or an orthopedist is advisable for these situations. It is important, however, that the physician be aware of what treatments are available and most effective, and of the indications for referral.

As for heat treatment, elastic stretch gloves may relieve symptoms through their warming and massaging effects.⁴

Some drugs for hand osteoarthritis got conditional recommendations in favor

The expert panel gave conditional recommendations in favor of:

- Topical capsaicin
- Topical NSAIDs
- Oral NSAIDs (including both nonselec-

A conditional recommendation means that most informed patients would want the treatment—but many would not

- tive and selective agents)
- Tramadol (Ultram)
 - Topical rather than oral NSAIDs for patients age 75 and older.

Other drug treatments got conditional recommendations against their use

The expert panel gave conditional recommendations against using:

- Intra-articular injections, and in particular, corticosteroid injections in the trapeziometacarpal (first carpometacarpal) joint
- Opioid analgesics
- Oral methotrexate or sulfasalazine in patients with erosive inflammatory interphalangeal osteoarthritis.

No recommendation for or against

- Hydroxychloroquine.

Comments—Intra-articular injections, opioids, and oral NSAIDs

I differ with these recommendations on several points.

Although the guidelines committee conditionally recommended against using intra-articular therapies for hand osteoarthritis, I find that intra-articular corticosteroid injections are often effective, particularly in patients who have inflammatory forms of the disease, ie, “erosive inflammatory osteoarthritis.” Most nonspecialist physicians probably have limited experience in giving injections into small joints, and referral to a rheumatologist or orthopedist would be appropriate.

I disagree as well with the conditional recommendation that intra-articular corticosteroid injections not be used for involvement of the trapeziometacarpal (first carpometacarpal) joint. I find that many patients with osteoarthritis of this joint experience improvement with intra-articular corticosteroid injections.

I agree that there are limited data on the use of intra-articular hyaluronan injections in this situation and do not routinely use them in this joint.

Opioid analgesics also received a conditional recommendation against their use. The same caveats apply here as for these drugs elsewhere.⁵ If used, opioids should be used at the lowest dose possible and for as short a time

as possible. If the physician is uncomfortable prescribing opioids for patients with osteoarthritis, referral to a pain specialist is recommended.

I disagree to some extent with the conditional recommendation that people age 75 and older should use topical rather than oral NSAIDs. I understand the recommendation, given that older people have a higher frequency of gastrointestinal, renal, and cardiac disease and are best served by avoiding NSAIDs. However, we all see patients over age 75 who are physiologically younger than their numerical age. Accordingly, I feel that the judgment of the physician plays a role in whether NSAIDs are reasonable for some older patients.

The committee recommended not using oral methotrexate or sulfasalazine in patients with erosive inflammatory interphalangeal osteoarthritis. I have used oral hydroxychloroquine off-label in such patients and find that they respond in a very rewarding fashion.

Given that this is an off-label use of hydroxychloroquine, the drug should be used only with appropriate consideration and after discussion with the patient about toxicity, especially about the risk of ocular manifestations.

■ OSTEOARTHRITIS OF THE KNEE

Some nondrug therapies got strong recommendations

The expert panel strongly recommended:

- Exercise (aerobic, resistance, land-based, and aquatic)
- Weight loss (for patients who are overweight).

Other nondrug therapies got conditional recommendations

The panel conditionally recommended:

- Self-management programs
- Manual therapy in combination with supervised exercise
- Psychosocial interventions
- Medially directed patellar taping
- Medially wedged insoles (if the patient has lateral compartment osteoarthritis)
- Laterally wedged subtalar strapped insoles (if the patient has medial compartment os-

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- teoarthritis)
- Heat therapy
 - Walking aids, as needed
 - Tai chi
 - Chinese acupuncture
 - Transcutaneous electrical nerve stimulation.

Comments: The ACR panel appropriately noted that Chinese acupuncture or transcutaneous electrical stimulation should be recommended only if the patient has chronic moderate to severe pain and is a candidate for total knee arthroplasty but is unwilling to undergo the procedure or has comorbid medical conditions that rule out surgery.

Nondrug therapies for knee osteoarthritis that got no recommendation for or against

- Balance exercise
- Laterally wedged insoles
- Manual therapy alone
- Knee braces
- Laterally directed patellar taping.

Comments. It was somewhat surprising that there were no recommendations about laterally wedged insoles or knee braces. Laterally wedged insoles have been recommended for patients who have medial compartment knee osteoarthritis⁶; being thinner at the in-step and thicker at the outer edge of the foot, they reduce load on the medial aspect of the knee. One has to be cautious in using knee wedging in patients who have concomitant ankle or hip angle deformities, lest these joints be compromised.

Some of these treatments would be out of the realm of the nonspecialist physician.

Conditional recommendations for initial drug therapy for knee osteoarthritis

The panel conditionally recommended that patients who have osteoarthritis of the knee use one of the following:

- Acetaminophen (contained in Tylenol and a host of other products)
- Oral NSAIDs
- Topical NSAIDs (with a strong recommendation for topical NSAIDs rather than oral NSAIDs in patients age 75 and older)
- Tramadol
- Intra-articular corticosteroid injections.

Comments. In the past, it was recommend-

ed that acetaminophen in full doses of up to 4,000 mg per day be considered.⁷ Current dogma, however, is that doses of acetaminophen should not exceed 3,000 mg per day to avoid damaging the liver. This concern led the US Food and Drug Administration (FDA) in 2011 to advise that the maximum daily dose be limited.⁸ The ACR panel recommended that patients be counseled to avoid all other products that contain acetaminophen, which is especially cogent, given the presence of this agent in many over-the-counter medications.⁹

The panel conditionally recommended that people age 75 and older use topical rather than oral NSAIDs. As mentioned earlier, a specific age limit does not take into account that many people age 75 and older may actually be physiologically younger than some in their 50s or 60s. Accordingly, it is recommended that the physician use judgment in this regard so that NSAIDs will not be denied to patients for whom they might be of significant value.

Strong recommendation for gastric protection in patients at risk on NSAIDs

If a patient with knee osteoarthritis has a history of a symptomatic or complicated upper gastrointestinal ulcer but has not had an upper gastrointestinal bleed in the past year and the physician chooses to prescribe an oral NSAID, the expert panel strongly recommended using either a cyclooxygenase (COX)-2-selective inhibitor or a nonselective NSAID in combination with a proton pump inhibitor.

Comment. The suggestion that patients who have had a complicated upper gastrointestinal ulcer in the past year could be considered for treatment with a COX-2-selective inhibitor or nonselective NSAID in combination with a proton pump inhibitor seemed a bit aggressive. My own inclination would be to avoid both nonselective and selective inhibitors in this situation. Alternative agents such as acetaminophen in full doses, tramadol, intra-articular hyaluronan injections, and intra-articular corticosteroid injections seem preferable with respect to safety in such patients.

The suggestion that a proton pump inhibitor be used whenever an NSAID is given for chronic management of knee or hip osteoar-

Current dogma is that doses of acetaminophen should not exceed 3,000 mg per day

thritis is reasonable.^{10,11} Although some studies have suggested that chronic use of proton pump inhibitors may predispose to osteopenia or osteoporosis, others have not, and gastric protection should be considered in patients at gastrointestinal risk.

Strong recommendation against ibuprofen in patients taking aspirin

The ACR panel strongly recommended that ibuprofen (Advil) not be prescribed to patients with knee osteoarthritis who are using aspirin in low doses for cardioprotection, and strongly recommended using another nonselective NSAID plus a proton pump inhibitor instead. The panel also strongly recommended against using a COX-2-selective inhibitor in this situation.^{12,13}

Comment. The rationale for these recommendations is that ibuprofen may render aspirin ineffective as a cardioprotective agent. Ibuprofen interferes with the aspirin-binding site on platelets, so that the protective effect of aspirin is lost.^{14,15} Celecoxib (Celebrex)¹⁶ and diclofenac (Voltaren) have binding sites different from that of aspirin, although the ACR recommends against using COX-2-selective inhibitors such as celecoxib in the situation and gives no recommendation about other NSAIDs.

No recommendations for or against

The panel issued no recommendations for or against the following treatments for patients with knee osteoarthritis:

- Intra-articular hyaluronan injections
- Duloxetine (Cymbalta)
- Opioid analgesics.

Comments on knee injections

Intra-articular injections of corticosteroids or hyaluronan are commonly used for knee osteoarthritis. As noted, corticosteroid injections received a conditional recommendation, while hyaluronan injections received no recommendation for or against.

How often to inject corticosteroids? In general, too-frequent injection of corticosteroids is to be avoided, in view of the risk of promoting joint breakdown. There is no “magic” number of injections that is safe, although more than 4 per year in the same joint

should generally be avoided. In some situations, however, repeat injections may be reasonable if alternative therapies are associated with higher risk.

Raynauld et al,¹⁷ in a randomized, double-blind, placebo-controlled trial, demonstrated that intra-articular corticosteroid injections at 3-month intervals for 2 years were not deleterious to knees.

My philosophy is generally not to inject on a regular basis, but to be selective and be guided by the patient’s clinical condition and response to prior injections.

Are hyaluronan injections effective? Although experts differ in their enthusiasm for intra-articular hyaluronan injections in the knee, I have found that many patients benefit from this treatment. Multiple studies have found it efficacious and safe overall.^{18–21} However, some systematic reviews have called its efficacy into question.⁷

Although differences in efficacy have been noted, this therapy was approved as being useful in patients with knee osteoarthritis in the Osteoarthritis Research Society International (OARSI) recommendations.⁷ The effect sizes were smaller in later assessments.²²

Hyaluronan injections do not pose the risk of joint breakdown that corticosteroid injections do, but their clinical efficacy is not as dramatic. Adverse reactions to most intra-articular hyaluronans are limited, with slight increases in pain and stiffness after injection. Significant inflammatory reactions characterized as “postinjection flares” are more commonly seen with high-molecular-weight cross-linked preparations. These reactions can be severe and can mimic joint infection clinically. Joint aspiration with synovial fluid analysis and culture may be necessary to exclude infection. Response to aspiration and nonsteroidal inflammatory agents or intra-articular corticosteroids is usually excellent.

Ultrasonographic guidance. As with intra-articular injections in other areas, ultrasonographic guidance is becoming more common, as it allows for more accurate drug administration.

Pes anserine bursitis must be ruled out as a cause of the patient’s knee symptoms—misdiagnosis is not uncommon. The bursa is located on the medial aspect of the tibia, and

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inflammation of the bursa is a common cause of pain in this area. Local steroid injection is extremely effective in symptomatic therapy. Physical therapy and NSAIDs may be adequate to treat milder cases.

Conditional recommendation against glucosamine, chondroitin, capsaicin

The ACR panel conditionally recommended that patients with knee osteoarthritis not use:

- Chondroitin sulfate
- Glucosamine
- Topical capsaicin.

Comment. Evidence is mixed about the efficacy of glucosamine and chondroitin sulfate, which are so-called nutraceuticals. Some studies found them useful^{23–25} but some did not,²⁶ and a meta-analysis concluded that they do not help.²⁷ The OARSI guidelines published in 2008 stated that these agents may relieve symptoms of osteoarthritis of the knee.⁷ The OARSI update published in 2010 found that glucosamine was effective, but less so than in previous studies.²² If glucosamine is effective, some studies suggest that glucosamine sulfate is more effective than glucosamine hydrochloride.²²

The same OARSI review revealed that chondroitin sulfate relieved pain but with heterogeneous, dissimilar effect sizes. Of interest was the finding that the 5-year incidence of total knee replacement was lower in patients treated with glucosamine sulfate 1,500 mg/day than with placebo. Also, the rate of decline of joint space narrowing was reported to be reduced in chondroitin sulfate-treated patients.²²

In practice, a conditional recommendation against a treatment means that most informed patients would not want the treatment, but some would. Accordingly, if patients still want to take chondroitin or glucosamine after being informed of the limited evidence of benefit, I feel a trial of their use is reasonable.

■ OSTEOARTHRITIS OF THE HIP

Indications for therapy of osteoarthritis of the hip are similar to those for osteoarthritis of the knee.

As in the knee, nonpharmacologic therapies are important. Loss of weight for overweight patients is extremely important; su-

pervised exercise is especially valuable. Use of canes or crutches as needed is conditionally recommended.

Pharmacologic management is similar to that of osteoarthritis of the knee, with particular use of acetaminophen, NSAIDs, tramadol, and intra-articular corticosteroid injections.

Comment. Intra-articular injection of corticosteroids into the hip would be out of the realm of most nonspecialist practices. Although some rheumatologists are expert in such injections, this treatment is generally best left to an orthopedist or invasive radiologist. The use of ultrasonographic guidance is becoming more frequent, with many rheumatologists having developed expertise in this approach to the knee and the hip. Since most studies were in patients with osteoarthritis of the knee, fewer data are available as to the efficacy of these agents in patients with hip osteoarthritis.

Fewer data are available also with respect to the benefit of chondroitin sulfate and glucosamine in patients with osteoarthritis of the hip. Total joint replacement is extremely effective if conservative therapy does not help.

■ FIRST, DO NO HARM

Guidelines from the ACR,^{1,2} the European League Against Rheumatism (EULAR),^{28,29} the American Academy of Orthopedic Surgeons (AAOS),³⁰ and the OARSI^{7,22} all differ somewhat, owing to the different evidence available at the time each guideline was developed and to different geographic and cultural backgrounds.

The compositions of these various panels also differ sufficiently to affect their overall recommendations. For example, the EULAR panel consisted of only rheumatologists and an orthopedic surgeon; for the hand osteoarthritis recommendations they added a physiatrist and two allied health professionals.^{28,29} The OARSI panel included two primary care physicians in addition to rheumatologists and an orthopedic surgeon.⁷ The ACR was the only professional society to include primary care physicians, physiatrists, and geriatricians along with rheumatologists, an orthopedic surgeon, and physical and occupational therapists.

Hyaluronan injections do not pose the risk of joint breakdown that corticosteroid injections do, but their efficacy is not as dramatic

Although it is to be expected that there will not be universal agreement on all points of management of osteoarthritis by diverse groups, it is essential that input from all these experts representing various subspecialties be recognized. Therapeutic approaches will vary depending on patient characteristics and the experience of the treating physician. As long as therapy is based on reasonable supportive data, beneficial effects can be anticipated.

Therapies that received conditional recommendations are not to be discounted if a reasonable percent of patients respond in positive fashion. Obviously, strong recommendations are more likely to be universally accepted since the likelihood that they will be beneficial is stronger.

In any approach to therapy, the caveat *primum non nocere*—first, do no harm—must always be kept in mind. ■

REFERENCES

1. Hochberg MC, Altman RD, April KT, et al; American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of non-pharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)* 2012; 64:465–474.
2. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. *Arthritis Rheum* 2000; 43:1905–1915.
3. Atkins D, Best D, Briss PA, et al; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004; 328:1490.
4. Askari A, Moskowitz RW, Ryan C. Stretch gloves. A study of objective and subjective effectiveness in arthritis of the hands. *Arthritis Rheum* 1974; 17:263–265.
5. Chou R, Fanciullo GJ, Fine PG, et al; American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain* 2009; 10:113–130.
6. Fang MA, Taylor CE, Nouvong A, Masih S, Kao KC, Perell KL. Effects of footwear on medial compartment knee osteoarthritis. *J Rehabil Res Dev* 2006; 43:427–434.
7. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 2008; 16:137–162.
8. US Food and Drug Administration (FDA). FDA Drug Safety Communication: Prescription Acetaminophen Products to be Limited to 325 mg Per Dosage Unit; Boxed Warning Will Highlight Potential for Severe Liver Failure. January 13, 2011. <http://www.fda.gov/Drugs/DrugSafety/ucm239821.htm>. Accessed November 28, 2012.
9. Schilling A, Corey R, Leonard M, Eghtesad B. Acetaminophen: old drug, new warnings. *Cleve Clin J Med* 2010; 77:19–27.
10. Bolten WW. Rational use of nonsteroidal anti-inflammatory drugs and proton pump inhibitors in combination for rheumatic diseases. *Orthopedic Research and Reviews* 2010; 2:75–84.
11. Graham DY, Agrawal NM, Campbell DR, et al; NSAID-Associated Gastric Ulcer Prevention Study Group. Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs: results of a double-blind, randomized, multicenter, active- and placebo-controlled study of misoprostol vs lansoprazole. *Arch Intern Med* 2002; 162:169–175.
12. American College of Rheumatology Ad Hoc Group on Use of Selective and Nonselective Nonsteroidal Antiinflammatory Drugs. Recommendations for use of selective and nonselective nonsteroidal antiinflammatory drugs: an American College of Rheumatology white paper. *Arthritis Rheum* 2008; 59:1058–1073.
13. Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA; American Heart Association. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. *Circulation* 2007; 115:1634–1642.
14. Ellison J, Dager W. Recent FDA warning of the concomitant use of aspirin and ibuprofen and the effects on platelet aggregation. *Prev Cardiol* 2007; 10:61–63.
15. Schuijt MP, Huntjens-Fleuren HW, de Metz M, Vollaard EJ. The interaction of ibuprofen and diclofenac with aspirin in healthy volunteers. *Br J Pharmacol* 2009; 157:931–934.
16. Wilner KD, Rushing M, Walden C, et al. Celecoxib does not affect the antiplatelet activity of aspirin in healthy volunteers. *J Clin Pharmacol* 2002; 42:1027–1030.
17. Raynauld JP, Buckland-Wright C, Ward R, et al. Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2003; 48:370–377.
18. Berenbaum F, Grifka J, Cazzaniga S, et al. A randomised, double-blind, controlled trial comparing two intra-articular hyaluronic acid preparations differing by their molecular weight in symptomatic knee osteoarthritis. *Ann Rheum Dis* 2012; 71:1454–1460.
19. Colen S, van den Bekerom MP, Mulier M, Haverkamp D. Hyaluronic acid in the treatment of knee osteoarthritis: a systematic review and meta-analysis with emphasis on the efficacy of different products. *BioDrugs* 2012; 26:257–268.
20. Wang CT, Lin J, Chang CJ, Lin YT, Hou SM. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials. *J Bone Joint Surg Am* 2004; 86-A:538–545.
21. Rutjes AW, Jüni P, da Costa BR, Trelle S, Nuesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Ann Intern Med* 2012; 157:180–191.
22. Zhang W, Nuki G, Moskowitz RW, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage* 2010; 18:476–499.
23. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage* 2007; 15:981–1000.
24. Towheed TE, Maxwell L, Anastassiades TP, et al. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev* 2005; 2:CD002946.
25. Vlad SC, LaValley MP, McAlindon TE, Felson DT. Glucosamine for pain in osteoarthritis: why do trial results differ? *Arthritis Rheum* 2007; 56:2267–2277.
26. Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med* 2006; 354:795–808.
27. Wandel S, Jüni P, Tendal B, et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ* 2010; 341:c4675.
28. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, et al. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis* 2003; 62:1145–55. Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis* 2005; 64:669–681.
29. Zhang W, Doherty M, Leeb BF, et al. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007; 66:377–388.
30. American Academy of Orthopaedic Surgeons. Treatment of osteoarthritis of the knee (non-arthroplasty). Rosemont, IL: American Academy of Orthopaedic Surgeons; 2008.

ADDRESS: Roland W. Moskowitz, MD, MS, 32050 Pinetree Road, Pepper Pike, OH 44124; e-mail Roland.Moskowitz@UHhospitals.org.