

Osteoarthritis: Rapid Evidence Review

Mark H. Ebell, MD, MS, University of Georgia College of Public Health, Athens, Georgia

Osteoarthritis (OA) should be suspected in patients with pain in the fingers, shoulders, hips, knees, or ankles, especially if they are older than 40 years. Patients older than 50 years who have joint pain, minimal morning stiffness, and functional impairment likely have OA. Radiography can confirm the diagnosis and may be helpful before surgical referral, but findings generally do not correlate well with symptoms. Exercise, physical therapy, knee taping, and tai chi are beneficial for knee OA. Medical therapy provides modest benefits in pain reduction and functional improvement; however, nonsteroidal anti-inflammatory drugs, tramadol, and other opioids have significant potential harms. Joint replacement may be considered for patients with moderate to severe pain and radiographically confirmed OA. Corticosteroid injections may be helpful in the short term. Vitamin D supplements, shoes specifically designed for persons with OA, antioxidant supplements, physical therapy for hip OA, ionized wrist bracelets, lateral wedge insoles for medial knee OA, and hyaluronic acid injections are not effective. (*Am Fam Physician*. 2018;97(8):523-526. Copyright © 2018 American Academy of Family Physicians.)

Osteoarthritis (OA) is a condition commonly encountered in primary care. This article provides a brief summary and review of the best available patient-oriented evidence for OA.

Epidemiology

The prevalence of OA by age is shown in *Table 1*.¹ Risk factors include:

- Older age (especially older than 50 years)
- Female sex
- Overweight or obesity
- Previous joint injury
- Job that requires bending or squatting
- Family history
- Participation in sports associated with repetitive impact (e.g., soccer, American football).²

Diagnosis

- OA should be suspected in patients with pain in the fingers, shoulders, hips, knees, or ankles, especially if they are older than 40 years.^{2,3}
- Alternative diagnoses should be considered in patients with inflammation, erythema, or pain that increases or changes significantly.
- The differential diagnosis includes collagen vascular disease, gout and pseudogout, trauma, septic arthritis, ankylosing spondylitis, and psoriatic arthritis.

SIGNS AND SYMPTOMS

Signs and symptoms that are common in OA include:

- Pain that is typically worse later in the day and relieved by rest.
- Joint swelling and tenderness, with or without crepitus.
- Bony enlargement in prolonged or severe OA.
- Joint pain, minimal morning stiffness, and functional impairment in patients older than 50 years.^{2,3} The presence of these findings is moderately helpful in ruling in OA, but their absence does not rule it out³ (*Table 2*).⁴
- Older age, obesity, difficulty walking down stairs, and clinical findings of decreased range of motion, effusion, and crepitus in patients with knee pain.⁵

CME This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz on page 503.

Author disclosure: Dr. Ebell is cofounder and editor-in-chief of Essential Evidence Plus, published by Wiley-Blackwell, Inc.

Patient information: A handout on this topic is available at <https://familydoctor.org/condition/osteoarthritis>.

TABLE 1

Prevalence of OA and Activity Limitation Due to OA

Age (years)	Prevalence of physician-diagnosed OA (%)	Prevalence of activity limitation due to OA (%)
18 to 44	7.3	2.7
45 to 64	30	13
65 and older	50	22

OA = osteoarthritis.
Information from reference 1.

- Lateral wedge insoles are ineffective for medial knee OA.¹⁹
- Knee bracing has insufficient evidence to draw conclusions about its effectiveness.²⁰
- Physical therapy was not beneficial for hip OA in a well-designed trial.²¹
- Weight loss has been recommended for patients with knee and hip OA²²; however, a systematic review found only low-quality evidence that bariatric surgery reduces pain and improves function in morbidly obese persons with knee pain.²³
- Ginger consumption significantly reduced pain and disability in five studies (N = 593) included in a systematic review.²⁴ However, patients were more likely to stop taking it, and the overall quality of studies was moderate. Similarly, avocado unsaponifiables may be effective at dosages of 300 to 600 mg per day. Both of these interventions, although likely safe, are limited by the small number and methodologic flaws of studies.²⁵

DIAGNOSTIC TESTING

- Radiography is not required to diagnose OA in patients with risk factors and typical symptoms.³
- Radiographic findings in patients with OA do not always correlate well with symptoms. Two studies found that only 16% of patients with frequent hip pain had radiographic evidence of OA; conversely, only 21% of patients who met the radiographic criteria for hip OA had frequent pain.⁶
- Typical radiographic findings in patients with OA include joint space narrowing, osteophytes, and subchondral sclerosis.
- Radiography can be helpful before referral for joint replacement, as radiographic severity is an important factor in determining whether surgery is appropriate.
- Magnetic resonance imaging detects joint abnormalities in about 90% of both obese and nonobese adults older than 50 years who do not have joint pain.⁷

Treatment

Figure 1 presents a suggested approach to the treatment of OA. Several therapies are supported by good-quality evidence. However, some widely used treatments (e.g., hyaluronic acid injections, arthroscopic surgery) are not effective and should be abandoned.

EXERCISE, DIET, AND PHYSICAL THERAPY

- Aquatic exercise has small short-term benefits for OA.⁸
- Vitamin D supplements, antioxidant supplements, shoes specifically designed for persons with OA, and ionized wrist bracelets are ineffective for OA.⁹⁻¹³
- Exercise, tai chi, knee taping, and physical therapy are beneficial for knee OA and can be recommended based on patient preference and acceptability.¹⁴⁻¹⁸

MEDICAL THERAPY

- Acetaminophen is less effective than nonsteroidal anti-inflammatory drugs (NSAIDs) for OA, but given its safety, a trial at an adequate dosage is appropriate.^{26,27}
- Of the NSAIDs currently available in the United States, diclofenac, 150 mg per day, is most likely to be effective for OA, followed by naproxen, according to a systematic review.²⁶ A Cochrane review concluded that topical diclofenac and ketoprofen are moderately effective.²⁸
- Topical capsaicin appeared to be somewhat effective in several small trials, although it is associated with a transient burning sensation.²⁹⁻³²

BEST PRACTICES IN ORTHOPEDICS

Recommendations from the Choosing Wisely Campaign

Recommendation	Sponsoring organization
Do not use glucosamine and chondroitin to treat patients with symptomatic osteoarthritis of the knee.	American Academy of Orthopaedic Surgeons
Do not use lateral wedge insoles to treat patients with symptomatic medial compartment osteoarthritis of the knee.	American Academy of Orthopaedic Surgeons

Source: For more information on the Choosing Wisely Campaign, see <http://www.choosingwisely.org>. For supporting citations and to search Choosing Wisely recommendations relevant to primary care, see <https://www.aafp.org/afp/recommendations/search.htm>.

TABLE 2

Accuracy of Key Signs and Symptoms for the Diagnosis of Knee OA

Clinical finding	Positive likelihood ratio	Negative likelihood ratio	Percentage of patients with OA when clinical findings are present or absent (45 to 64 years of age; pretest probability = 30%)		Percentage of patients with OA when clinical findings are present or absent (65 years and older; pretest probability = 50%)	
			Present	Absent	Present	Absent
Bony enlargement	3.3	0.6	59	20	77	38
Functional limitation	3.2	0.7	58	23	76	41
Pain during flexion	2.8	0.8	55	26	74	44
Heberden nodes (hard or bony swellings in the distal interphalangeal joint)	2.0	0.9	46	28	67	47

OA = osteoarthritis.

Information from reference 4.

- Tramadol is moderately effective for OA, according to a systematic review of 11 randomized trials (N = 1,019), and has a number needed to treat (NNT) of 6 for one person to report at least moderate improvement.³³ Conversely, the number needed to harm (NNH) for one person to stop taking tramadol because of adverse effects is 8.
- Duloxetine (Cymbalta) is a serotonin–norepinephrine reuptake inhibitor approved for treatment of painful conditions. Its NNT is 7 for clinically significant pain reduction in OA.^{34,35} The most common adverse effect is mild to moderate nausea (23% vs. 7% for placebo; NNH = 6).³⁶
- Because tramadol and duloxetine have harms and adverse effects similar in magnitude to their potential benefits, they should be used only in select patients.
- Propoxyphene (not available in the United States) plus acetaminophen is no better than acetaminophen alone, has more adverse effects, and should be avoided.³⁷
- Oral and transdermal opioids (not including tramadol) have only modest benefits that are of questionable clinical significance, according to a Cochrane review.³⁸ These medications also have significant adverse effects, and long-term use is discouraged. Patients taking opioids should be closely monitored, and the dose should be kept as low as possible. Daily dosages of more than 50 mg of hydrocodone or 30 mg of oxycodone are discouraged.³⁹
- In general, it is reasonable to begin treatment with full-dose acetaminophen and/or topical therapy and progress to an NSAID such as naproxen or diclofenac, then, if necessary, to tramadol or duloxetine.

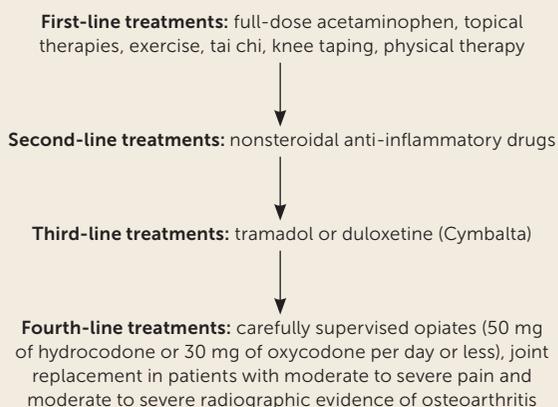
SURGICAL THERAPY

- Joint replacement is an option for patients with moderate to severe pain and radiographically confirmed OA.⁴⁰ A randomized trial found that patients with moderate radiographically confirmed knee OA had significantly

improved pain and function after joint replacement compared with those receiving usual care, although serious adverse effects can occur, including deep venous thrombosis, infection, and the need for further surgery or mobilization under anesthesia.⁴¹ Obese and nonobese patients have similar outcomes after knee replacement.^{42–44}

- Arthroscopic meniscectomy with or without debridement is no more effective than sham procedures or exercise for knee OA, according to a systematic review of nine studies (N = 1,279).⁴⁵ It is also ineffective for patients with degenerative meniscal tears.⁴⁶
- Corticosteroid injections improve function and provide short-term pain relief, but do not improve overall quality of life, according to systematic reviews.^{47,48} A recent large

FIGURE 1



Suggested treatment approach to the patient with osteoarthritis.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References
Radiography can confirm the diagnosis of OA and may be helpful before surgical referral, but findings tend not to correlate well with symptoms.	C	6, 7
Exercise, physical therapy, knee taping, and tai chi are beneficial for knee OA.	B	14-18
Ineffective treatments for OA include vitamin D and antioxidant supplements, shoes specifically designed for persons with OA, lateral wedge insoles for medial knee OA, physical therapy for hip OA, ionized wrist bracelets, and hyaluronic acid injections.	B	9-13, 19, 21, 50-52
Medical therapy for OA should begin with full-strength acetaminophen and topical therapy, then proceed to nonsteroidal anti-inflammatory drugs and selectively to tramadol and other opioids. Nonsteroidal anti-inflammatory drugs and opioids may reduce pain and improve function, but have significant potential harms.	A	26-36
Joint replacement should be considered for patients with moderate to severe pain and radiographically confirmed OA.	A	40, 41
Corticosteroid injections may be helpful in the short term, but evidence is mixed.	B	47-49

OA = osteoarthritis.

A = consistent, good-quality patient-oriented evidence; **B** = inconsistent or limited-quality patient-oriented evidence; **C** = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <https://www.aafp.org/afpsort>.

randomized trial found no benefit and greater cartilage loss in patients receiving corticosteroid injections.⁴⁹

- Hyaluronic acid injections are not effective for OA, according to a review of the highest-quality studies and unpublished research.⁵⁰⁻⁵²
- Dextrose prolotherapy injections showed a modest benefit for knee OA in two small randomized trials, but the evidence base is limited, and the technique may be operator-dependent and not easily reproduced.^{53,54}
- Platelet-rich plasma or bone marrow aspirate concentrate injections are not effective for OA.^{55,56}

COMPLEMENTARY THERAPY

The following complementary therapies have been studied for the treatment of OA:

- Acupuncture is at best minimally effective for OA of the knee or hip.⁵⁷⁻⁵⁹
- Oral glucosamine with or without chondroitin does not appear to be effective in well-designed trials.⁶⁰⁻⁶²
- S-adenylmethionine and methylsulfonylmethane have uncertain effectiveness based on systematic reviews.^{63,64} Observed benefits were small in magnitude and probably not clinically significant.

Prognosis

Symptoms of OA tend to progress over time, although they may temporarily improve in the short term.

Editor's Note: Rapid Evidence Review is a new article format that was created with the goal of providing key clinical information that can be read quickly and that answers questions at the point of care. These articles are unique in that the references are only available online and the SORT table recommendations are linked to the corresponding areas of the text in the online version of the article. Please let us know what you think of the new format by commenting online or e-mailing us at afpedit@afp.org.

Data Sources: This article was based on literature cited in Essential Evidence Plus, the Cochrane database, recently published InfoPOEMs, and a PubMed search using the Clinical Queries database for the term osteoarthritis. Search date: July 2017.

The Author

MARK H. EBELL, MD, MS, is a professor in the Department of Epidemiology at the University of Georgia College of Public Health, Athens.

Address correspondence to Mark H. Ebell, MD, MS, University of Georgia College of Public Health, 150 Yonah Dr., Athens, GA 30601. Reprints are not available from the author.

References

References for this article are available online at <https://www.aafp.org/afp/2018/0415/p523.html>.

References

1. Centers for Disease Control and Prevention (CDC). Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation—United States, 2010–2012. *MMWR Morb Mortal Wkly Rep*. 2013;62(44):869–873.
2. Felson DT, Lawrence RC, Dieppe PA, et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med*. 2000;133(8):635–646.
3. Zhang W, Doherty M, Peat G, et al. EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. *Ann Rheum Dis*. 2010;69(3):483–489.
4. Claessens AA, Schouten JS, van den Ouweland FA, Valkenburg HA. Do clinical findings associate with radiographic osteoarthritis of the knee? *Ann Rheum Dis*. 1990;49(10):771–774.
5. Peat G, Thomas E, Duncan R, et al. Estimating the probability of radiographic osteoarthritis in the older patient with knee pain. *Arthritis Rheum*. 2007;57(5):794–802.
6. Kim C, Nevitt MC, Niu J, et al. Association of hip pain with radiographic evidence of hip osteoarthritis: diagnostic test study. *BMJ*. 2015;351:h5983.
7. Guermazi A, Niu J, Hayashi D, et al. Prevalence of abnormalities in knees detected by MRI in adults without knee osteoarthritis: population based observational study (Framingham Osteoarthritis Study). *BMJ*. 2012;345:e5339.
8. Bartels EM, Juhl CB, Christensen R, et al. Aquatic exercise for the treatment of knee and hip osteoarthritis. *Cochrane Database Syst Rev*. 2016;(3):CD005523.
9. Hinman RS, Wrigley TV, Metcalf BR, et al. Unloading shoes for self-management of knee osteoarthritis: a randomized trial. *Ann Intern Med*. 2016;165(6):381–389.
10. Canter PH, Wider B, Ernst E. The antioxidant vitamins A, C, E and selenium in the treatment of arthritis: a systematic review of randomized clinical trials. *Rheumatology (Oxford)*. 2007;46(8):1223–1233.
11. Jin X, Jones G, Cicuttini F, et al. Effect of vitamin D supplementation on tibial cartilage volume and knee pain among patients with symptomatic knee osteoarthritis: a randomized clinical trial. *JAMA*. 2016;315(10):1005–1013.
12. McAlindon T, LaValley M, Schneider E, et al. Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis. *JAMA*. 2013;309(2):155–162.
13. Bratton RL, Montero DP, Adams KS, et al. Effect of “ionized” wrist bracelets on musculoskeletal pain: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc*. 2002;77(11):1164–1168.
14. Bosomworth NJ. Exercise and knee osteoarthritis: benefit or hazard? *Can Fam Physician*. 2009;55(9):871–878.
15. Song R, Lee EO, Lam P, Bae SC. Effects of tai chi exercise on pain, balance, muscle strength, and perceived difficulties in physical functioning in older women with osteoarthritis: a randomized clinical trial. *J Rheumatol*. 2003;30(9):2039–2044.
16. Thomas KS, Muir KR, Doherty M, Jones AC, O’Reilly SC, Bassey EJ. Home based exercise programme for knee pain and knee osteoarthritis: randomised controlled trial. *BMJ*. 2002;325(7367):752.
17. Deyle GD, Henderson NE, Matekel RL, Ryder MG, Garber MB, Allison SC. Effectiveness of manual physical therapy and exercise in osteoarthritis of the knee. A randomized, controlled trial. *Ann Intern Med*. 2000;132(3):173–181.
18. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee: a Cochrane systematic review. *Br J Sports Med*. 2015;49(24):1554–1557.
19. Parkes MJ, Maricar N, Lunt M, et al. Lateral wedge insoles as a conservative treatment for pain in patients with medial knee osteoarthritis: a meta-analysis. *JAMA*. 2013;310(7):722–730.
20. Duijvenvoorden T, Brouwer RW, van Raaij TM, Verhagen AP, Verhaar JA, Bierma-Zeinstra SM. Braces and orthoses for treating osteoarthritis of the knee. *Cochrane Database Syst Rev*. 2015;(3):CD004020.
21. Bennell KL, Egerton T, Martin J, et al. Effect of physical therapy on pain and function in patients with hip osteoarthritis: a randomized clinical trial. *JAMA*. 2014;311(19):1987–1997.
22. Gay C, Chabaud A, Guillely E, Coudeyre E. Educating patients about the benefits of physical activity and exercise for their hip and knee osteoarthritis. Systematic literature review. *Ann Phys Rehabil Med*. 2016;59(3):174–183.
23. Groen VA, van de Graaf VA, Scholtes VA, Sprague S, van Wagenveld BA, Poolman RW. Effects of bariatric surgery for knee complaints in (morbidly) obese adult patients: a systematic review. *Obes Rev*. 2015;16(2):161–170.
24. Bartels EM, Folmer VN, Bliddal H, et al. Efficacy and safety of ginger in osteoarthritis patients: a meta-analysis of randomized placebo-controlled trials. *Osteoarthritis Cartilage*. 2015;23(1):13–21.
25. Christensen R, Bartels EM, Astrup A, Bliddal H. Symptomatic efficacy of avocado-soybean unsaponifiables (ASU) in osteoarthritis (OA) patients: a meta-analysis of randomized controlled trials. *Osteoarthritis Cartilage*. 2008;16(4):399–408.
26. da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet*. 2017;390(10090):e21–e33.
27. Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. *BMJ*. 2015;350:h1225.
28. Derry S, Wiffen PJ, Kalso EA, et al. Topical analgesics for acute and chronic pain in adults – an overview of Cochrane reviews. *Cochrane Database Syst Rev*. 2017;(5):CD008609.
29. De Silva V, El-Metwally A, Ernst E, Lewith G, Macfarlane GJ; Arthritis Research UK Working Group on Complementary and Alternative Medicines. Evidence for the efficacy of complementary and alternative medicines in the management of osteoarthritis: a systematic review. *Rheumatology (Oxford)*. 2011;50(5):911–920.
30. Deal CL, Schnitzer TJ, Lipstein E, et al. Treatment of arthritis with topical capsaicin: a double-blind trial. *Clin Ther*. 1991;13(3):383–395.
31. Kosuwon W, Sirichatiwapee W, Wisanuyotin T, Jeeravipoolvarn P, Laupattarakasem W. Efficacy of symptomatic control of knee osteoarthritis with 0.0125% of capsaicin versus placebo. *J Med Assoc Thai*. 2010;93(10):1188–1195.
32. McCarthy GM, McCarty DJ. Effect of topical capsaicin in the therapy of painful osteoarthritis of the hands. *J Rheumatol*. 1992;19(4):604–607.
33. Cepeda MS, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis: a systematic review and meta-analysis. *J Rheumatol*. 2007;34(3):543–555.
34. Wang ZY, Shi SY, Li SJ, et al. Efficacy and safety of duloxetine on osteoarthritis knee pain: a meta-analysis of randomized controlled trials. *Pain Med*. 2015;16(7):1373–1385.

OSTEOARTHRITIS

35. Citrome L, Weiss-Citrome A. A systematic review of duloxetine for osteoarthritic pain: what is the number needed to treat, number needed to harm, and likelihood to be helped or harmed? *Postgrad Med*. 2012;124(1):83-93.
36. Brunton S, Wang F, Edwards SB, et al. Profile of adverse events with duloxetine treatment: a pooled analysis of placebo-controlled studies. *Drug Saf*. 2010;33(5):393-407.
37. Li Wan Po A, Zhang WY. Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol [published corrections appear in *BMJ*. 1998;316(7125):116 and *BMJ*. 1998;316(7132):656]. *BMJ*. 1997;315(7122):1565-1571.
38. da Costa BR, Nüesch E, Kasteler R, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip. *Cochrane Database Syst Rev*. 2014;(9):CD003115.
39. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016 [published correction appears in *MMWR Recomm Rep*. 2016;65(11):295]. *MMWR Recomm Rep*. 2016;65(1):1-49.
40. Escobar A, Quintana JM, Aróstegui I, et al. Development of explicit criteria for total knee replacement. *Int J Technol Assess Health Care*. 2003;19(1):57-70.
41. Skou ST, Roos EM, Laursen MB, et al. A randomized, controlled trial of total knee replacement. *N Engl J Med*. 2015;373(17):1597-1606.
42. Amin AK, Patton JT, Cook RE, Brenkel IJ. Does obesity influence the clinical outcome at five years following total knee replacement for osteoarthritis? *J Bone Joint Surg Br*. 2006;88(3):335-340.
43. Cavaignac E, Lafontan V, Reina N, et al. Obesity has no adverse effect on the outcome of unicompartmental knee replacement at a minimum follow-up of seven years [published correction appears in *Bone Joint J*. 2013;95-B(11):1582]. *Bone Joint J*. 2013;95-B(8):1064-1068.
44. Chen JY, Lo NN, Chong HC, et al. The influence of body mass index on functional outcome and quality of life after total knee arthroplasty. *Bone Joint J*. 2016;98-B(6):780-785.
45. Thorlund JB, Juhl CB, Roos EM, Lohmander LS. Arthroscopic surgery for degenerative knee: systematic review and meta-analysis of benefits and harms. *BMJ*. 2015;350:h2747.
46. Khan M, Evaniew N, Bedi A, Ayeni OR, Bhandari M. Arthroscopic surgery for degenerative tears of the meniscus: a systematic review and meta-analysis. *CMAJ*. 2014;186(14):1057-1064.
47. Arroll B, Goodyear-Smith F. Corticosteroid injections for osteoarthritis of the knee: meta-analysis. *BMJ*. 2004;328(7444):869.
48. Jüni P, Hari R, Rutjes AW, et al. Intra-articular corticosteroid for knee osteoarthritis. *Cochrane Database Syst Rev*. 2015;(10):CD005328.
49. McAlindon TE, LaValley MP, Harvey WF, et al. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. *JAMA*. 2017;317(19):1967-1975.
50. Rutjes AW, Jüni P, da Costa BR, Trelle S, Nüesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Ann Intern Med*. 2012;157(3):180-191.
51. Navarro-Sarabia F, Coronel P, Collantes E, et al.; AMELIA study group. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. *Ann Rheum Dis*. 2011;70(11):1957-1962.
52. Jevsevar D, Donnelly P, Brown GA, Cummins DS. Viscosupplementation for osteoarthritis of the knee: a systematic review of the evidence. *J Bone Joint Surg Am*. 2015;97(24):2047-2060.
53. Rabago D, Patterson JJ, Mundt M, et al. Dextrose prolotherapy for knee osteoarthritis: a randomized controlled trial [published correction appears in *Ann Fam Med*. 2013;11(5):480]. *Ann Fam Med*. 2013;11(3):229-237.
54. Reeves KD, Hassanein K. Randomized prospective double-blind placebo-controlled study of dextrose prolotherapy for knee osteoarthritis with or without ACL laxity. *Altern Ther Health Med*. 2000;6(2):68-74, 77-80.
55. Khoshbin A, Leroux T, Wasserstein D, et al. The efficacy of platelet-rich plasma in the treatment of symptomatic knee osteoarthritis: a systematic review with quantitative synthesis. *Arthroscopy*. 2013;29(12):2037-2048.
56. Shapiro SA, Kazmerchak SE, Heckman MG, Zubair AC, O'Connor MI. A prospective, single-blind, placebo-controlled trial of bone marrow aspirate concentrate for knee osteoarthritis. *Am J Sports Med*. 2017;45(1):82-90.
57. Hinman RS, McCrory P, Pirota M, et al. Acupuncture for chronic knee pain: a randomized clinical trial. *JAMA*. 2014;312(13):1313-1322.
58. Lin X, Huang K, Zhu G, Huang Z, Qin A, Fan S. The effects of acupuncture on chronic knee pain due to osteoarthritis: a meta-analysis. *J Bone Joint Surg Am*. 2016;98(18):1578-1585.
59. Kwon YD, Pittler MH, Ernst E. Acupuncture for peripheral joint osteoarthritis: a systematic review and meta-analysis. *Rheumatology (Oxford)*. 2006;45(11):1331-1337.
60. Wilkens P, Scheel IB, Grundnes O, Hellum C, Storheim K. Effect of glucosamine on pain-related disability in patients with chronic low back pain and degenerative lumbar osteoarthritis: a randomized controlled trial. *JAMA*. 2010;304(1):45-52.
61. Rozendaal RM, Koes BW, van Osch GJ, et al. Effect of glucosamine sulfate on hip osteoarthritis: a randomized trial. *Ann Intern Med*. 2008;148(4):268-277.
62. Roman-Blas JA, Castañeda S, Sánchez-Pernaute O, Largo R, Herrero-Baumont G; CS/GS Combined Therapy Study Group. Combined treatment with chondroitin sulfate and glucosamine sulfate shows no superiority over placebo for reduction of joint pain and functional impairment in patients with knee osteoarthritis: a six-month multicenter, randomized, double-blind, placebo-controlled clinical trial. *Arthritis Rheumatol*. 2017;69(1):77-85.
63. Rutjes AW, Nüesch E, Reichenbach S, Jüni P. S-Adenosylmethionine for osteoarthritis of the knee or hip. *Cochrane Database Syst Rev*. 2009;(4):CD007321.
64. Brien S, Prescott P, Lewith G. Meta-analysis of the related nutritional supplements dimethyl sulfoxide and methylsulfonylmethane in the treatment of osteoarthritis of the knee. *Evid Based Complement Alternat Med*. 2011;2011:528403.