# Nonoperative Options for Management of Articular Cartilage Disease

Sourav K. Poddar, MD[a,b,*], Luke Widstrom, DO[a]

**KEYWORDS**

• Viscosupplementation • Cartilage • Osteoarthritis • Corticosteroid • Glucosamine • NSAIDs

**KEY POINTS**

- Low-impact exercise and weight loss are beneficial for osteoarthritis of weight-bearing joints.
- Judicious use of nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen can be appropriate for pain management.
- Topical NSAIDs may be a treatment option with fewer side effects than their oral counterpart.
- Viscosupplementation injections are useful for mild to moderate knee osteoarthritis.
- Corticosteroid injections are useful for short-term pain relief.

## INTRODUCTION

Articular cartilage damage is a major cause of pain and functional disability which can occur as a result of injury, disease process such as osteoarthritis, or both. While surgical approaches may provide definitive treatment, they are not typically indicated for mild to moderate damage, may be contraindicated in patients with risk factor, and carry a risk of both operative and anesthetic complications. Nonoperative care may not be definitive in advanced cases, however it can provided definitive treatment in more mild to moderate disease. When excluding biologic options, nonoperative treatments do not reverse the disease process or damage, however there are a variety of options which have been shown to provide significant improvement in terms of pain and function, and many treatments delay and can potentially stall progression of articular cartilage damage. In this chapter, we provide an evidence based approach to the various nonoperative options for the treatment of articular cartilage disease, including

Disclosure Statement: The authors have nothing to disclose.
[a] Department of Family Medicine, University of Colorado School of Medicine, Aurora, CO, USA;
[b] Department of Orthopedics, University of Colorado School of Medicine, Aurora, CO, USA
* Corresponding author. CU Sports Medicine Center, 2000 South Colorado Boulevard, Tower One, Suite 4500, Denver, CO 80222.
*E-mail address:* sourav.poddar@ucdenver.edu

Clin Sports Med ■ (2017) ■–■
http://dx.doi.org/10.1016/j.csm.2017.02.003 **sportsmed.theclinics.com**

exercise, weight loss, physical therapy, braces, oral medications, topical medications, supplements, corticosteroid injections, viscosupplementation, and prolotherapy.

### *Exercise*

Among nonpharmacologic treatments of osteoarthritis (OA), exercise is one of the most consistently recommended modalities in national and international guidelines. Exercise has been shown to decrease symptoms of OA, improve joint function, and prevent disability.[1] Modalities that are recommended include both land-based and water-based training, as well as strength, flexibility, and endurance training. The Osteoarthritis Research Society International has made recommendations in favor of land-based exercise, water-based exercise, and strength training, all based on good-quality evidence taken from systematic reviews and meta-analyses of randomized controlled trials (RCTs).[2]

A 2015 systematic review of 54 RCTs assessed the immediate and short-term effects of exercise on knee OA.[3] High-quality evidence demonstrated a mean 12-point reduction in pain on a 0 to 100 scale immediately following exercise. Additionally, exercise improved function by an equivalent of 10 points. Twelve studies included in the review analyzed the sustainability of treatment effect after cessation of formal treatment for both pain and physical function over a 2-month to 6-month period. An equivalent reduction of 6 points on the pain scale and improvement of 3 points on the function scale were noted.

A similar systematic review published in 2014 analyzed 10 RCTs pertaining to the treatment benefits of land-based exercise for hip OA.[4] Although not as marked as the effect for knee OA, a significant improvement in both pain and physical function was noted. Pain was reduced by 8 points with exercise, and physical function was improved by 7 points. These improvements were both sustained for 3 to 6 months after the cessation of treatment in the 5 studies that followed patients for this duration.

Thirteen RCTs were included in the most recent systematic review assessing the benefits of aquatic based therapy for both knee and hip OA.[5] Twelve of the studies showed a significant decrease in pain scores by a mean of 5 points and an improvement in disability by a mean of 5 points. Ten of the studies additionally found a mean 7-point higher score on quality of life compared with the control group.

### *Weight Loss*

As a person's weight increases, there is an associated increase in joint pain symptoms and severity.[6] In addition, there is an elevated risk of developing OA with weight gain, up to 36% for every 5 kg. Weight gain can also accelerate the progression of OA and lead to greater severity of disease. This has been demonstrated in cadaveric studies.

However, weight loss has been shown to decrease physical disability due to OA, and meta-analysis has shown that this effect can be predictably reproduced with only a 5% weight reduction over a 20-week period.[7] In addition, pain has been demonstrated to be reduced with weight loss, although a dose-response relationship has not been established. When weight loss is maintained, the benefits of pain reduction continue to be significant, and this has been shown to be true when assessed over a year after initial weight reduction.[8] The improvement in pain and function associated with weight loss may be partially due to a significant reduction in joint compressive forces and inflammatory cytokines.[9] For example, every decrease in 1 kg of weight leads to a 2.2 kg decrease in peak knee load.[10] Notably, this is independent of the effects of exercise, as weight loss due to diet has been shown to have a greater reduction in the aforementioned measures when compared with weight loss due to exercise.[9] Interestingly, this decrease in joint loads and proinflammatory cytokines is seen with increased walking speed. Weight loss has also

demonstrated reduced rates of articular cartilage thickness loss and improved articular cartilage quality (as measured by proteoglycan content)[11] in medial compartment knee OA. This has been measured with as little as a 7% reduction in body weight.

The significant benefits of weight loss when measured against the low risks associated have led to strong recommendations in favor of weight loss for overweight persons with OA from multiple organizations including the Osteoarthritis Research Society International (OARSI) and American College of Rheumatology (ACR).[1]

### *Physical Therapy/Strength Training*

One of the most commonly prescribed treatments for articular cartilage disease is physical therapy. Physical therapy includes many methods and modalities, but the component that has the highest level of evidence is strength training. Strength training is one of the core treatments deemed appropriate for all individuals in the OARSI guidelines for nonsurgical management of knee OA.[2] Improved strength can lead to decreased joint loading and increased joint stability.[12] A 2011 systematic review on the effect of strength training for knee OA showed moderate effect size for both decreasing pain and improving function.[2]

Few studies evaluate the effectiveness of physical therapy for delaying progression of OA to the endpoint of joint replacement. A recent RCT of 109 participants with 6-year follow-up compared rates of hip replacement for patients with OA who performed a strengthening, flexibility, and functional exercise program to those who had education alone.[13] At 6 years, survival of the native hip was 44% in the treatment group compared with 25% in the control group, and the mean time to joint replacement was 5.4 years compared with 3.5 years.

Results for investigations evaluating other modalities used in physical therapy, such as transcutaneous electrical nerve stimulation units and therapeutic ultrasound range from showing no benefit to mixed evidence in low-quality studies, and as such these modalities are not recommended.[2,14]

### *Bracing*

Various braces and other biomechanical interventions, such as compression sleeves, foot orthoses, and canes, are used by patients with articular cartilage disease to provide additional structural support in attempts to alleviate pain and improve function. Unloader braces in particular may be used in the knee when either the lateral or medial compartment is predominantly involved in an attempt to offload the affected compartment and distribute forces more evenly. Although in some instances this can make a significant difference, there may be drawbacks to use as unloader braces can be uncomfortable, fit poorly, and limit higher level activities. The evidence for biomechanical interventions overall is inconclusive for benefits in the realms of pain, function, stiffness, and quality of life.[15] There is a lack of agreement among the various major guidelines for the use of these assistive devices for OA.[1] However, as these are low risk interventions, they may be worth a trial with shared decision making. The OARSI recommends the use of biomechanical interventions for knee OA as directed by an appropriate specialist.[2] However, cane use is not recommended for patients with multiple joint involvement as it may increase the weight-bearing load on other affected joints to alleviate knee pain.

## ORAL MEDICATIONS: ACETAMINOPHEN, NONSTEROIDAL ANTI-INFLAMMATORY DRUGS, OPIOIDS

When patients are no longer experiencing sufficient symptom relief from nonpharmacologic methods, either oral or topical analgesics are typically initiated as an

adjunctive therapy. A logical first choice is acetaminophen due to greater safety and a lower side-effect profile than nonsteroidal anti-inflammatory drugs (NSAIDs). As such, it is consistently recommended as a first-line pharmacologic treatment option.[1] There is low-level evidence on the effectiveness of acetaminophen for OA pain in the short term.[2] A conservative dosing regimen for pain relief as needed and with activity is typically recommended with a maximum dose limited to 3 g a day.

For patients with inflammatory OA, or for those with an inadequate response to acetaminophen, oral NSAIDs can be used either in place of or as an adjunct to acetaminophen. Evidence suggests that NSAIDs are more effective for moderate to severe OA in terms of pain reduction and improvement in functional status.[16] However, this needs to be weighed against the increased risk of gastrointestinal and renal side effects. Gastrointestinal effects may be mitigated by using the cyclo-oxygenase-2 selective inhibitor celecoxib, which has a similar rate to acetaminophen.[17] The rate of cardiac and vascular side effects for celecoxib is higher than placebo, but similar to most nonselective NSAIDs other than naproxen, which has the lowest risk.[18] However, celecoxib, as opposed to the nonselective NSAIDs, has not been demonstrated to have a significantly greater treatment effect than acetaminophen.[17] When considering the gastrointestinal risks of NSAID, providers may contemplate concomitantly initiating a proton pump inhibitor for gastroprotection in patients with moderate comorbidity risk. This has been shown to reduce the rate of endoscopically detected gastroduodenal ulcers.[2] Oral NSAIDs are generally not recommended for patients with high comorbidity risk.

Opioid pain medication is sometimes used for patients with pain from articular cartilage disease that is refractory to acetaminophen, NSAIDs, and injections. However, a 2014 Cochrane review of opioids for knee and hip OA found only a 0.7-cm difference between opioids and placebo on a 0 to 10-cm visual analog pain scale.[19] The difference for function was only 0.6 units on the 0 to 10 WOMAC disability scale. This questionable clinical relevance is contrasted by a significant risk of withdrawal and serious adverse events. As a result, opioids are typically reserved only for patients who have failed all other nonoperative treatments and who are not surgical candidates. In such instances, opioids should be provided under the close observation of a primary care provider, low-potency opioids should be used, and dose escalation should be avoided.

## TOPICALS: NONSTEROIDAL ANTI-INFLAMMATORY DRUGS, LIDOCAINE, CAPSAICIN

Another option for patients who want to try pharmacologic treatment but wish to minimize systemic effects is topical therapy. Topical treatments deliver local analgesic effects with minimal systemic absorption. Options include topical NSAIDs, such as diclofenac, lidocaine, and capsaicin. A 2016 Cochrane review evaluated 33 RCTs on topical NSAIDs for chronic musculoskeletal pain due to OA.[20] In studies ranging 6 to 12 weeks, 60% of patients had a significant decrease in pain compared with placebo carrier. However, 50% of patients had similar results with the placebo carrier, showing only a 10% increase in success rate with topical compared with placebo. There was a slight increase in local skin reactions with topical NSAIDs but no increase in gastrointestinal adverse effects compared with placebo. The OARSI recommends topical NSAIDs for patients with knee-only OA but is uncertain for multiple joint involvement.[2]

Capsaicin is the active ingredient in hot chili pepper. When applied locally, it enhances the release of substance P from pain nerve fibers, such that it is rapidly depleted and decreases pain signal transmission.[21] Good evidence has demonstrated

that it is superior to placebo for pain reduction, but at the increased risk of local irritation, with up to fourfold number of patients withdrawing from trials due to this.[2] Drug residue on the hands can lead to mucous membrane, eye, and skin irritation in other areas if care is not taken during application.

## SUPPLEMENTS: GLUCOSAMINE, CHONDROITIN, OTHERS

Many patients with articular cartilage disease wishing to avoid traditional pharmacologic treatments or their associated side effects turn to over-the-counter supplements. Two of the most commonly used supplements are glucosamine and chondroitin sulfate, either alone or in combination. The estimated $810 million US consumer market for the 2 supplements in 2005 demonstrates the extent of use.[22] The rationale behind glucosamine use is related to its presence in human articular cartilage. Glucosamine is an aminosaccharide used for the synthesis of glycosaminoglycans and glycoproteins, and is highly concentrated in connective tissues, especially cartilage. Chondroitin is a glycosaminoglycan found in the extracellular matrix of articular cartilage.[23] In vitro studies demonstrate that it increases type II collagen and proteoglycan synthesis in human articular chondrocytes, reduce inflammation, and improve the anabolic/catabolic balance of the extracellular matrix.[24]

Despite the prevalence of glucosamine and chondroitin in human articular cartilage and the promising in vitro effects, studies analyzing pain and disease progression have had mixed results. A 2005 systematic review of 25 RCTs comparing glucosamine with placebo for OA found no difference in pain improvement when only considering the high-quality studies, but did show a 22% improvement when including all studies.[25] The same review found statistical improvements in function in the glucosamine group using the Lequesne index but not the WOMAC index. There was no statistical difference from placebo in terms of adverse reactions. A recent meta-analysis evaluated the effectiveness of glucosamine and chondroitin sulfate for chondroprotection. Two of 3 trials used glucosamine sulfate, and both of those trials found a decreased loss of joint space on radiographs and decreased odds of experiencing OA progression compared with placebo.[26] This is in agreement with prior meta-analyses that found small to moderate protective effects on joint space narrowing at 3 years.[27] This was not found to be the case in the trial using glucosamine hydrochlorate.[26]

A 2015 Cochrane review analyzing the effect of chondroitin for OA found improved pain scores compared with placebo but with high heterogeneity and low-level evidence.[28] Small but statistically significant improvement in function was demonstrated, as was a decreased loss of joint space compared with placebo. Additionally, the number of adverse events was statistically similar to placebo. A recent double-blinded RCT demonstrated statistically significant reduction in cartilage volume loss in knee medial compartment OA at 2 years compared with celecoxib.[29]

Patients who are interested in taking supplements should be counseled that glucosamine and chondroitin may be beneficial for pain and function, but the effect may be small and the evidence is of low quality. The evidence for chondroprotection for both supplements is of moderate to high quality. Glucosamine sulfate has better evidence than glucosamine hydrochlorate for this purpose. Given these findings and the low risk, both supplements may be worth a trial, but the benefits may take months to years to be realized.

Fish oil is another supplement commonly used by patients with OA. Fish oil is a source of omega-3 fatty acids and has anti-inflammatory properties.[30] The benefits of fish oil for the treatment of rheumatoid arthritis (RA) are well accepted and it has been shown to reduce pain scores and the use of other medications. Due to its

efficacy in RA, it has been extrapolated that fish oil may have benefit in OA, especially with its anti-inflammatory function. Most studies, however, have either been in vitro, showing reduced inflammatory cartilage destruction, or in vivo animal studies, with an example being noticeable improvement of signs of pain in dogs. Few human RCTs have been performed. A 2015 meta-analysis found only 6 such studies since 1992, with significantly varying endpoints and methods of evaluation and predominantly low quality.[30] The results were mixed with some studies showing no benefit, some showing modest benefit, and some showing significant benefit. More high-quality studies are needed in this area before any recommendations can be made.

## STEROID INJECTIONS

Although it has been described as a degenerative process, current understanding of the pathophysiology of OA involves a cascade of inflammatory mediators in the joint. Corticosteroid injections are performed with the intention of reducing pain and improving function by producing a powerful local anti-inflammatory effect.[31] The effects of corticosteroid injections are most notable in the short term, resulting in significant decreases in pain.[2] This makes steroid injections a reasonable option for acute flares of OA or other causes of acute onset pain due to articular cartilage insult. The benefits after 1 to 6 weeks, however, are unclear.[31] Hyaluronic acid injections have greater evidence for longer duration relief.[32] However, from a practical clinical standpoint, many insurance companies require failure of corticosteroid injections before a trial of viscosupplementation. This often results in the use of a trial of corticosteroid injections for OA even if long-term relief from chronic pain is the desired effect.

There is a paucity of data comparing the efficacy of the various corticosteroids. The presence of only a small number of high-quality RCTs and mixed results prevents the establishment of firm conclusions to guide treatment.[33]

The most common side effects of corticosteroid injection are injection site pain, elevated blood sugar, and rarely skin atrophy.[33] However, a Cochrane review indicated that placebo injections resulted in higher rates of side effects than corticosteroids.[31] The rate of joint infection when using sterile technique has been estimated at approximately 1 in 22,000 injections.[34] There is some concern that steroid injections may accelerate cartilage loss. This may be due to animal studies with rabbits in which frequent administration and high dosages demonstrated this effect. However, other animal studies have had mixed results, and in some instances have shown beneficial effects on cartilage structure.[35] One study comparing triamcinolone acetonide injections to saline injections in the knee every 3 months for 2 years showed no difference in joint space loss.[36]

## VISCOSUPPLEMENTATION

Viscosupplementation is a technique that involves the injection of exogenous high molecular weight hyaluronic acid molecules to combat the effect of the decreased viscoelasticity of synovial fluid seen in OA.[37] It is typically the second-line choice for injection therapy if the effectiveness of corticosteroids is limited. It is also used without prior corticosteroid injections for younger, physically active patients. Viscosupplementation is a good alternative in situations in which corticosteroid injections are contraindicated, such as with labile diabetes mellitus, or in the setting of adverse reaction or allergy to steroid preparations. Although pain relief from viscosupplementation is usually slower in onset than corticosteroid injections, it typically confers longer-lasting pain relief, and may be a better intermediate-term option due to its decreased side-effect profile.[32]

In addition to the traditionally understood biomechanical model of viscosupplementation increasing joint lubrication and shock absorption by providing improved viscoelasticity, several other mechanisms for pain reduction are at play. It has been shown to stimulate endogenous production of hyaluronic acid by synovial cells.[37] It may also have an anti-inflammatory effect by blocking production of prostaglandin E2 and release of arachidonic acid. Research suggests it might have a direct analgesic on intra-articular nociceptors. Finally, viscosupplementation may offer a protective effect against cell damage from oxygen free radicals and phagocytosis.[38]

A 2006 Cochrane review of 76 RCTs on viscosupplementation for knee OA concluded that it is an effective treatment with beneficial effects for pain, function, and patient global assessment.[32] This was most notable at the 5-week to 13-week period for pain with weight bearing. When compared with placebo, the effect size at some time points was moderate to large. However, the onset, duration, and magnitude of effect varied between the various products and time points of administration.

In 2016 the American Medical Society for Sports Medicine released a position statement on the use of hyaluronic acid injections for knee OA based on the results of a meta-analysis of literature comparing hyaluronic acid injections to corticosteroid injections and placebo injections.[39] The meta-analysis evaluated studies that determined a significant clinical response based on the Outcome Measures in Rheumatoid Arthritis Clinical Trials-ORSI (OMERACT-OARSI) criteria. They found that compared with steroid and placebo injections, hyaluronic acid injections led to a 15% and 11% higher response rate, respectively. This led to a recommendation in favor of hyaluronic acid injections for appropriate patients with mild to moderate knee OA.

Viscosupplementation for joints other than the knee has less robust evidence, generally with insufficient evidence to make recommendations for or against use.[40] For example, a recent systematic review of hyaluronic acid injections for ankle OA found that although it is safe and effective, it was no more effective than other conservative treatments.[41] Although a recent meeting of 8 European experts on OA led to a unanimous vote in favor of the effectiveness of viscosupplementation for mild to moderate knee OA, there was only moderate consensus in favor for hip and ankle, and weak consensus in favor for shoulder OA.[42] The OARSI deemed hyaluronic acid injections for hip OA as not appropriate.[2]

## PROLOTHERAPY (AND BIOLOGICS)

Prolotherapy is an injection technique that uses nonbiologic irritant solutions, most commonly dextrose.[43] The mechanism of action is multifactorial and not well understood, but proposed mechanisms include stimulation of a local healing process in tissue with chronic damage, decreasing joint instability by increasing the strength of tendons and ligaments, and stimulating cell proliferation.[44] Animal studies have suggested cartilage-specific anabolic growth. A recent small study used arthroscopic second look after treatment along with staining for chondrocyte growth and biopsy of sites with increased stain uptake.[43] The biopsies revealed a mixture of fibrocartilage and hyalinelike cartilage.

A recent meta-analysis of 4 RCTs demonstrated that peri-articular and intra-articular hypertonic dextrose prolotherapy is superior to exercise alone for improvement in pain and function in knee OA, meeting criteria for statistically significant and clinically relevant effect, but with moderate heterogeneity.[44] A 2013 RCT with 90 participants compared dextrose prolotherapy with saline injections and exercise for knee OA.[45] At 52 weeks, the prolotherapy arm had a significant improvement over the saline and exercise arms in the 100-point WOMAC composite score, which evaluates knee

pain, function, and stiffness. The prolotherapy group had a mean improvement of 15.3 points compared with 7.6 and 8.2 for the saline and exercise groups. Although prolotherapy may be an effective form of treatment for OA, patient discomfort with needle sticks, lack of insurance coverage, and finding a prolotherapist provide treatment challenges.[46]

Other biologic treatment options, such as platelet rich plasma and bone marrow aspirate concentrate/stem cells are also currently used for the treatment of OA. These provide a fertile environment for further study and are covered in detail in the article (see Matthew J. Kraeutler and colleagues' article, "Biologic Options for Articular Cartilage Wear (Platelet-Rich Plasma, Stem Cells, Bone Marrow Aspirate Concentrate)," in this issue).

## SUMMARY

Nonoperative options for articular cartilage injury are omnipresent but have not shown to be curative. Recommendations for low-impact exercise and weight loss provide benefit and are a foundation for the treatment of OA. Many options are available to manage the pain associated with OA and their use should be based on an individualized consideration of the risks and benefits afforded the patient. Future studies to individualize treatment options based on patient phenotype and genotype may hold promise.

## REFERENCES

1. Nelson AE, Allen KD, Golightly YM, et al. A systematic review of recommendations and guidelines for the management of osteoarthritis: the chronic osteoarthritis management initiative of the U.S. bone and joint initiative. Semin Arthritis Rheum 2014;43(6):701–12.
2. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014;22(3):363–88.
3. Fransen M, McConnell S, Harmer AR, et al. Exercise for osteoarthritis of the knee. Cochrane Database Syst Rev 2015;(1):CD004376.
4. Fransen M, McConnell S, Hernandez-Molina G, et al. Exercise for osteoarthritis of the hip. Cochrane Database Syst Rev 2014;(4):CD007912.
5. 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.
6. Vincent HK, Heywood K, Connelly J, et al. Obesity and weight loss in the treatment and prevention of osteoarthritis. PM R 2012;4(5 Suppl):S59–67.
7. Christensen R, Bartels EM, Astrup A, et al. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. Ann Rheum Dis 2007;66(4):433–9.
8. Christensen R, Henriksen M, Leeds AR, et al. Effect of weight maintenance on symptoms of knee osteoarthritis in obese patients: a twelve-month randomized controlled trial. Arthritis Care Res (Hoboken) 2015;67(5):640–50.
9. Messier SP, Mihalko SL, Legault C, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. JAMA 2013;310(12):1263–73.
10. Aaboe J, Bliddal H, Messier SP, et al. Effects of an intensive weight loss program on knee joint loading in obese adults with knee osteoarthritis. Osteoarthritis Cartilage 2011;19(7):822–8.

11. Anandacoomarasamy A, Leibman S, Smith G, et al. Weight loss in obese people has structure-modifying effects on medial but not on lateral knee articular cartilage. Ann Rheum Dis 2012;71(1):26–32.
12. Nguyen C, Lefèvre-Colau MM, Poiraudeau S, et al. Rehabilitation (exercise and strength training) and osteoarthritis: a critical narrative review. Ann Phys Rehabil Med 2016;59(3):190–5.
13. Svege I, Nordsletten L, Fernandes L, et al. Exercise therapy may postpone total hip replacement surgery in patients with hip osteoarthritis: a long-term follow-up of a randomised trial. Ann Rheum Dis 2015;74(1):164–9.
14. Sharma L. Osteoarthritis year in review 2015: clinical. Osteoarthritis Cartilage 2016;24(1):36–48.
15. Duivenvoorden T, Brouwer RW, van Raaij TM, et al. Braces and orthoses for treating osteoarthritis of the knee. Cochrane Database Syst Rev 2015;(3):CD004020.
16. Towheed TE, Maxwell L, Judd MG, et al. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev 2006;(1):CD004257.
17. Bannuru RR, Schmid CH, Kent DM, et al. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Ann Intern Med 2015;162(1):46–54.
18. Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013;382(9894):769–79.
19. 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.
20. Derry S, Conaghan P, Da Silva JA, et al. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev 2016;(4):CD007400.
21. Rains C, Bryson HM. Topical capsaicin. A review of its pharmacological properties and therapeutic potential in post-herpetic neuralgia, diabetic neuropathy and osteoarthritis. Drugs Aging 1995;7(4):317–28.
22. Dahmer S, Schiller RM. Glucosamine. Am Fam Physician 2008;78(4):471–6.
23. Uebelhart D, Thonar EJ, Delmas PD, et al. Effects of oral chondroitin sulfate on the progression of knee osteoarthritis: a pilot study. Osteoarthritis Cartilage 1998;6(Suppl A):39–46.
24. Hochberg M, Chevalier X, Henrotin Y, et al. Symptom and structure modification in osteoarthritis with pharmaceutical-grade chondroitin sulfate: what's the evidence? Curr Med Res Opin 2013;29(3):259–67.
25. Towheed TE, Maxwell L, Anastassiades TP, et al. Glucosamine therapy for treating osteoarthritis. Cochrane Database Syst Rev 2005;(2):CD002946.
26. Gallagher B, Tjoumakaris FP, Harwood MI, et al. Chondroprotection and the prevention of osteoarthritis progression of the knee: a systematic review of treatment agents. Am J Sports Med 2015;43(3):734–44.
27. Lee YH, Woo JH, Choi SJ, et al. Effect of glucosamine or chondroitin sulfate on the osteoarthritis progression: a meta-analysis. Rheumatol Int 2010;30(3):357–63.
28. Singh JA, Noorbaloochi S, MacDonald R, et al. Chondroitin for osteoarthritis. Cochrane Database Syst Rev 2015;(1):CD005614.
29. Pelletier JP, Raynauld JP, Beaulieu AD, et al. Chondroitin sulfate efficacy versus celecoxib on knee osteoarthritis structural changes using magnetic resonance imaging: a 2-year multicentre exploratory study. Arthritis Res Ther 2016;18(1):256.
30. Boe C, Vangsness CT. Fish oil and osteoarthritis: current evidence. Am J Orthop (Belle Mead NJ) 2015;44(7):302–5.

31. Jüni P, Hari R, Rutjes AW, et al. Intra-articular corticosteroid for knee osteoarthritis. Cochrane Database Syst Rev 2015;(10):CD005328.
32. Bellamy N, Campbell J, Robinson V, et al. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev 2006;(2):CD005321.
33. Garg N, Perry L, Deodhar A. Intra-articular and soft tissue injections, a systematic review of relative efficacy of various corticosteroids. Clin Rheumatol 2014;33(12): 1695–706.
34. Pal B, Morris J. Perceived risks of joint infection following intra-articular corticosteroid injections: a survey of rheumatologists. Clin Rheumatol 1999;18(3):264–5.
35. Vandeweerd JM, Zhao Y, Nisolle JF, et al. Effect of corticosteroids on articular cartilage: have animal studies said everything? Fundam Clin Pharmacol 2015; 29(5):427–38.
36. 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(2):370–7.
37. Jackson DW, Evans NA, Thomas BM. Accuracy of needle placement into the intra-articular space of the knee. J Bone Joint Surg Am 2002;84-A(9):1522–7.
38. Presti D, Scott JE. Hyaluronan-mediated protective effect against cell damage caused by enzymatically produced hydroxyl (OH.) radicals is dependent on hyaluronan molecular mass. Cell Biochem Funct 1994;12(4):281–8.
39. Trojian TH, Concoff AL, Joy SM, et al. AMSSM scientific statement concerning viscosupplementation injections for knee osteoarthritis: importance for individual patient outcomes. Clin J Sport Med 2016;26(1):1–11.
40. Conrozier T. Optimizing the effectiveness of viscosupplementation in non-knee osteoarthritis. Joint Bone Spine 2016;83(1):1–2.
41. Faleiro TB, Schulz Rda S, Jambeiro JE, et al. Viscosupplementation in ankle osteoarthritis: a systematic review. Acta Ortop Bras 2016;24(1):52–4.
42. Henrotin Y, Raman R, Richette P, et al. Consensus statement on viscosupplementation with hyaluronic acid for the management of osteoarthritis. Semin Arthritis Rheum 2015;45(2):140–9.
43. Reeves KD, Sit RW, Rabago DP. Dextrose prolotherapy: a narrative review of basic science, clinical research, and best treatment recommendations. Phys Med Rehabil Clin N Am 2016;27(4):783–823.
44. Sit RW, Chung VCh, Reeves KD, et al. Hypertonic dextrose injections (prolotherapy) in the treatment of symptomatic knee osteoarthritis: a systematic review and meta-analysis. Sci Rep 2016;6:25247.
45. Rabago D, Patterson JJ, Mundt M, et al. Dextrose prolotherapy for knee osteoarthritis: a randomized controlled trial. Ann Fam Med 2013;11(3):229–37.
46. Slattengren AH, Christensen T, Prasad S, et al. PURLs: prolotherapy: a nontraditional approach to knee osteoarthritis. J Fam Pract 2014;63(4):206–8.