Current evidence for osteoarthritis treatments

Ananthila Anandacoomarasamy and Lyn March

Abstract: Osteoarthritis (OA) is the most common form of arthritis and the leading cause of chronic disability among older people. The burden of the disease is expected to rise with an aging population and the increasing prevalence of obesity. Despite this, there is as yet no cure for OA. However, in recent years, a number of potential therapeutic advances have been made, in part due to improved understanding of the underlying pathophysiology. This review provides the current evidence for symptomatic management of OA including nonpharmacological, pharmacological and surgical approaches. The current state of evidence for disease-modifying therapy in OA is also reviewed.

Keywords: osteoarthritis, management, non-pharmacological, pharmacological, surgical, symptom modification, disease modification

Introduction

Osteoarthritis (OA) is the most common form of arthritis and the leading cause of chronic disability among older people. More than 50% of people over the age of 65 years have radiological evidence of OA, with approximately 10% of men and 18% of women suffering symptomatic OA [Woolf and Pfleger, 2003]. In a recent population-based cohort study, the lifetime risk of symptomatic knee OA was 45% [Murphy *et al.* 2008].

Cartilage is a complex tissue comprised of an extensive extracellular matrix of water, type II collagen and aggrecan surrounding the cellular component, chondrocytes. A complex network of cytokines and growth factors secreted by synovial lining cells and chondrocytes controls the level of matrix synthesis and degradation [Felson, 2004]. A loss of homeostasis in the maintenance of healthy articular cartilage leads to the pathologic degeneration of articular cartilage in OA [Poole, 2002]. Although cartilage destruction is a central feature in OA, this is a disease of the whole joint in which all articular structures are affected. Hyaline cartilage loss is accompanied by bony remodeling, capsular stretching and weakness of peri-articular muscles [Felson, 2006]. In some patients, synovitis, ligamentous laxity and bone marrow lesions can be observed.

While synovial inflammation in OA is not as extensive as that observed in the classic inflammatory forms of arthritis such as rheumatoid arthritis, there is mounting evidence that cartilage destruction in OA is the result of cartilage inflammation at the molecular level [Loeser, 2006]. The degeneration is not simply wear and tear, although the mechanical issues are extremely important [Poole, 2002]. It is the combination of molecular damage and inability to effectively manage physical forces that leads to pathology. Abnormal mechanical forces stimulate the chondrocyte to produce a host of inflammatory mediators which include cytokines and chemokines [Loeser, 2006].

OA typically affects the knee, hip, cervical and lumbar spine, distal interphalangeal, proximal interphalangeal, carpometacarpal, and metatarsophalangeal joints. Almost everyone has structural evidence of OA on radiographs in at least one joint by the age of 70 [Felson, 2004]. Nevertheless, only a proportion of those with radiographic disease have symptoms. On the other hand, early painful OA may be unaccompanied by radiographic change. In addition, the severity of symptoms may not directly correlate with the severity of structural disease.

OA typically presents with progressive, insidious discomfort brought upon by activities such as walking, climbing, kneeling and typing. Joint stiffness and contracture may develop from osteophyte formation or synovitis and capsular scarring [Lonner, 2003]. Warmth, swelling and crepitus are associated features. With the

Correspondence to:
**Lyn March,
MBBS, FRACP, PhD, MSc,
FAFPHM**
Consultant
Rheumatologist &
Professor, Institute of
Bone and Joint Research,
Royal North Shore
Hospital, University of
Sydney, Sydney, Australia
lynmar@med.usyd.edu.au

**Ananthila
Anandacoomarasamy,
MBBS (Hons), BSc (Med),
FRACP**
Research Fellow, Institute
of Bone and Joint
Research, Royal North
Shore Hospital, University
of Sydney, Australia

Consultant
Rheumatologist, Staff
Specialist, Department of
Rheumatology, Concord
Hospital, Sydney, Australia

exception of end-stage disease, OA usually produces little or no pain at rest, which helps to distinguish it from inflammatory forms of arthritis [Lonner, 2003]. Hyaline articular cartilage contains no nociceptive fibres and therefore is not a source of pain [Felson, 2006]. Bone, synovial inflammation and a stretched joint capsule are likely to be sources of pain.

Management

Thus far, the management of clinical OA has largely relied on symptomatic interventions. While there is as yet no cure for OA, it has become clear that the management of risks and predisposing factors are vital in halting or retarding disease progression. Recent studies in the development of disease-modifying OA drugs (DMOADs) are also promising in the future management of OA. This review focuses on the current evidence for nonpharmacological, pharmacological and surgical management options of OA. Recently, evidence-based international consensus recommendations were developed by the OARSI (Osteoarthritis Research Society International) Treatment Guidelines Committee for the management of knee and hip OA [Zhang *et al.* 2008]. This report provides treatment recommendations based on the supporting level of evidence, which is derived from a systematic review of the recent literature [Zhang *et al.* 2008].

Benefits of therapy have been expressed as effect sizes (ES) which represent the magnitude of the mean difference between the intervention and the control groups after dividing by the standard deviation of the measures. This allows some comparison across therapies that have different outcome measures. Although a guide only, it has been suggested that $ES \leq 0.2$ represents a small effect, $ES \approx 0.5$ a medium effect and $ES \geq 0.8$ a large effect [Cohen, 1988]. This grading of ES corresponds to approximate numbers needed to treat of 13, five and three respectively assuming a response rate of 60% in the intervention group [Furukawa, 1999; Cohen, 1988].

Nonpharmacological and preventative strategies

Education, exercise and weight loss are mainstays in the management of OA and the promotion of general health. Patient education about treatment objectives and the importance of changes in lifestyle, exercise, weight reduction and other measures is supported by two meta-analyses but the ES for pain relief is small; 0.06 (0.02–0.10).

The recommendation that initial focus should be on self-help and patient-driven treatments rather than on passive therapies delivered by health professionals is based on expert opinion, common sense and economic considerations [Zhang *et al.* 2008].

Obesity is a significant risk factor for both the development and progression of tibio-femoral knee OA (both symptomatic and radiographic) [Hart *et al.* 1999; Cicuttini *et al.* 1997, 1996; Felson *et al.* 1997, 1992, 1988; Bagge *et al.* 1991]. An association, though modest, has also been demonstrated between obesity and OA at other sites such as the hip, hand and patello-femoral joint, suggesting that both mechanical and metabolic factors may be responsible for the link between OA and obesity. In the Framingham study, evaluation of 800 women showed a decrease in BMI of $\geq 2 \, kg/m^2$ in the preceding 10 years decreased the odds of developing symptomatic OA by >50% [Felson *et al.* 1992].

Recently, a large clinical trial, the Arthritis, Diet, and Activity Promotion Trial (ADAPT) study, randomized 316 overweight or obese older subjects with knee OA to exercise only (combined aerobic and strengthening), dietary weight loss only, exercise plus dietary weight loss or a healthy lifestyle control group. After 18 months, despite only modest reductions in body weight, significant improvements in pain and physical function were seen in the diet plus exercise group [Messier *et al.* 2004]. A second recent randomized clinical trial, evaluating a rapid weight loss diet among 80 patients with knee OA, found that a weight reduction of 10% improved function by 28% [Christensen *et al.* 2005]. The authors found that fewer than four patients would need to be treated with a low energy diet for one patient to achieve a ≥ 50% improvement in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC, a measure of joint pain, stiffness and function) when compared to a control diet. To date, there are no longitudinal studies evaluating if weight loss slows the progression of knee OA but this effect would appear to be clinically plausible. The pooled effect sizes for improvements in pain (ES = 0.20; CI 0–0.39) and physical disability (ES = 0.23; CI 0.04–0.42) are small with a mean weight reduction of 6.1 kg (range 4.7–7.6 kg) [Zhang *et al.* 2008]. There are no published randomized controlled trials (RCTs) for weight loss and hip OA.

Three systematic reviews evaluating the effect of exercise for hip and knee OA, have demonstrated improvement in pain, function, and global assessment [Roddy and Doherty, 2006]. However, data was pooled in these meta-analyses and included studies of all exercise types, taking no account of the nature of the exercise program (eg aerobic or strengthening). Relatively few comparisons between aerobic and strengthening exercises have been made, and both aerobic and strengthening exercises are effective for knee OA [Roddy and Doherty, 2006]. Pooled ESs for pain relief are in the moderate range for both aerobic (ES = 0.52; CI 0.34–0.70) and muscle strengthening exercises (ES = 0.32; CI 0.23–0.42) for OA knee [Zhang *et al.* 2008]. In an earlier Cochrane review assessing exercise in hip and knee OA, there were only two studies totaling 100 participants for hip OA [Fransen and McConnell 2008]. However, in a recent meta-analysis of all individual hip OA trials, exercise was found to be more effective, albeit modest, than attention control [Felson, 2009].

Exercise therapy for OA of the hip or knee should be individualized and patient-centered, taking into account factors such as age, comorbidity and overall morbidity. Group and home exercise are equally effective and patient preference should be considered. Hydrotherapy is also a useful adjunct to any exercise program. Adherence is the principal predictor of long-term outcome from exercise in patients with knee or hip OA [Roddy and Doherty, 2006]. Improvement in muscle strength and proprioception gained from exercise programmes may reduce the progression of knee and hip OA. The enhanced proprioception may also reduce falls risk.

A recent systematic review showed that acupuncture that met adequate criteria was significantly superior to both sham acupuncture and to no additional intervention in improving pain and function in patients with chronic knee pain [White *et al.* 2007]. However, there was heterogeneity amongst the eligible studies and further research is required to confirm these findings and provide more information on long-term effects. Another issue is that of the intensity of provider contact associated with acupuncture and the physiologic effect of needling [Scharf *et al.* 2006]. However, the technique is reasonably safe and well tolerated by most, although several sessions are usually required. A summary of the overall evidence showed moderate ESs

(ES = 0.51; CI 0.23–0.79) for pain, stiffness (ES = 0.41; CI 0.13–0.69) and function (ES = 0.51, CI 0.23–0.79) with a NNT of 4 (CI 3–9) for clinically significant relief of pain [Zhang *et al.* 2008].

Although assessment of footwear is recommended in most OA management guidelines, there is a paucity of evidence to support this [Roddy and Doherty, 2006]. Several observational studies of laterally wedged insoles for medial compartment knee OA have reported symptomatic improvement but not three RCTs. However, in a prospective 2-year RCT, the use of laterally wedged insoles was associated with reduced NSAID (nonsteroidal anti-inflammatory drugs) usage and better compliance [Pham *et al.* 2004a]. However, there was no alteration of pain, stiffness or function. There is little research evaluating medial wedged insoles for lateral compartment knee OA. The only RCT showed improved pain and function with the use of a rearfoot medial wedge compared to a neutral insole in women with valgus lateral compartment knee OA [Hinman and Bennell, 2009]. Further research is required for validation. There have been no controlled studies of footwear in hip OA. The following features have been suggested for footwear for people with OA: thick, soft, shock-absorbing sole; minimal heel-raise; broad forefoot to allow splaying of the toes during forefoot loading; and deep, soft uppers [Roddy and Doherty, 2006]. However, there have been no controlled studies to support this recommendation.

Evidence from randomized trials is sparse regarding the efficacy of therapies to correct malalignment across the knee joint [Felson, 2006]. In one trial, a significant reduction of knee pain was seen in those with medial compartment OA and varus malalignment, using a neoprene sleeve over the knee. Knee braces that stabilize the knee joint and provide a valgus stress have also been shown to improve pain and function in patients with medial compartment knee OA [Lonner, 2003]. Patello-femoral pain may be caused by tilting or malalignment of the patella [Felson, 2006]. Patellar realignment with the use of braces or tape may lessen pain. In clinical trials using tape, knee pain was reduced as compared to placebo.

A walking stick can be used to unload painful joints. There are no RCTs to support this but there was complete expert consensus that

walking aids can reduce pain in patients with hip and knee OA. This should be held in the contralateral hand at the level of the greater trochanter of the hip [Felson, 2006]. Use of compression gloves is helpful for stiffness and pain from osteoarthritic involvement of the distal and proximal interphalangeal joints [Barnsley, 2005]. A variety of splints are also available for the carpometacarpal joint.

Pharmacological therapies

Symptomatic measures

Simple analgesia. Both paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) are evidence-based drugs for symptom relief in OA [Bannwarth, 2006]. Paracetamol is the first-line pharmacologic agent for the treatment of OA recommended by all international guidelines [Zhang *et al.* 2005; Jordan *et al.* 2003]. A recent meta-analysis concluded that paracetamol is effective for pain relief in OA, albeit with a small effect size (ES = 0.21; 95% CI 0.02–0.41) [Zhang *et al.* 2004]. In the recent Cochrane review, paracetamol showed a statistically significant but small reduction in pain (ES = 0.13; CI 0.04–0.22) [Towheed *et al.* 2006]. However, there was no improvement in overall WOMAC, suggesting that it should not be expected to have a strong effect on stiffness or function. There was no significant difference in toxicity compared to placebo in short-term trials. However, given its comparatively favourable side-effect profile, it should remain the first-line pharmacologic agent.

NSAIDs are effective agents for the treatment of OA. A meta-analysis concluded that NSAIDs, including COX-2 selective inhibitors, can reduce pain and functional disability in knee OA better than placebo (ES = 0.32; 95% CI 0.24–0.39; ES = 0.29; 95% CI 0.18–0.40, respectively) [Bannwarth, 2006]. NSAIDs might be more effective in hip OA, based on a systematic review (ES = 0.69; 95% CI 0.12–1.26) [Bannwarth, 2006]. The long-term use of NSAIDs for OA is not advocated. Interestingly, in the meta-analysis including eight trials directly comparing paracetamol and NSAIDs, an aggregated effect size of 0.20 and 0.30 for pain relief and overall WOMAC index, respectively, were observed in favour of oral NSAIDs [Bannwarth, 2006]. There is high interindividual variability in patient response to both paracetamol and NSAIDs, but there are no recognized clinical predictors of response.

NSAIDs are associated with more adverse events than paracetamol in short-term trials, and confirmed in the recent Cochrane systematic review of short-term RCTs [Relative risk (RR) 1.47; 95% CI 1.08–2.00] [Zhang *et al.* 2008]. COX-2 selective inhibitors have been to shown to be as effective as conventional nonselective NSAIDs in patients with OA [Bannwarth, 2006]. They are associated with significantly fewer upper gastrointestinal (GI) complications, at least in patients not taking low-dose aspirin, and slightly less dyspepsia compared with conventional NSAIDs. While they are tolerated in most patients with aspirin-induced asthma, they have a pattern of nephrotoxicity and drug interactions similar to those of conventional NSAIDs [Bannwarth, 2006]. There is also no evidence that COX-2 selective inhibitors are less toxic to the GI tract than conventional NSAIDs combined with a proton-pump inhibitor (PPI), especially in patients at high risk of developing adverse GI events. Either of these is recommended in patients with increased GI risk [Hooper *et al.* 2004].

Recently, the cardiovascular risks of COX-2 selective inhibitors and NSAIDs have been extensively highlighted. A recent systematic review has shown that cardiovascular risk was increased with rofecoxib, diclofenac, indomethacin, and probably meloxicam [McGettigan and Henry, 2006]. Importantly, naproxen, with a pooled relative risk of 0.97 (95% CI 0.87–1.07), neither increased nor decreased risk (ie not cardioprotective as previously thought). Celecoxib increased risk at doses higher than 200 mg/day, while at lower doses, risk was not increased. However, the authors recommend caution in light of four studies published since completion of the meta-analysis [McGettigan and Henry, 2006]. They suggest that naproxen appears to be the safest NSAID from a cardiovascular perspective. It should be noted that lumaricoxib was not assessed in this meta-analysis. In another systematic review, the overall cardiovascular risk associated with COX-2 selective inhibitors was not significantly greater than that associated with conventional nonselective NSAIDS (RR = 1.19; 95% CI 0.80–1.75) [Hooper *et al.* 2004]. In a recent systematic review and meta-analysis of atherothrombotic complications of COX-2 selective inhibitors and nonselective NSAIDS, the

incidence of serious vascular events was 1% per annum in COX-2 selective inhibitor-treated patients compared with 0.9% in traditional NSAID-treated patients (RR 1.16; 95% CI 0.97–1.38) [Zhang *et al.* 2008]. However, the heterogeneity in risk among traditional NSAIDs was observed again (ie ibuprofen and diclofenac had modest increase in risk but not naproxen).

It should be noted that the European Agency for the Evaluation of Medicinal Products advises that COX-2 selective inhibitors are contraindicated in patients with ischaemic heart disease or stroke, and that caution should be exercised in patients with cardiovascular risk factors [Zhang *et al.* 2008]. In the opinion of the authors, for an individual with a higher risk of developing peptic ulcer disease, a short-course of a COX-2 selective inhibitor may be a reasonable option. In contrast, in one with high cardiovascular risk, if an anti-inflammatory has to be used, naproxen plus a PPI may be the safer option. In summary, NSAIDs are effective for symptom relief in OA, and should be prescribed at the lowest effective dose for the shortest possible duration.

Topical therapy. Short-term use of topical NSAIDS is safe and effective in OA of the hand and knee according to a 2004 meta-analysis [Biswal *et al.* 2006]. This was also confirmed in another meta-analysis in 2004 [Lin *et al.* 2004]. However, these were less effective than oral NSAIDs. In addition, there was possible publication bias as there was significant asymmetry of a funnel plot [Zhang *et al.* 2008]. Their efficacy in hip OA is questionable because of the depth of that joint. Four studies have assessed efficacy at 4 weeks or beyond in knee OA, finding a modest effect (ES = 0.28; 95% CI 0.14–0.42) [Biswal *et al.* 2006]. Topical NSAIDs are usually well-tolerated with systemic adverse effects being very uncommon. However, local adverse events can occur in 10–15% of patients.

Topical capsaicin, the active principle of hot chilli pepper, exerts its effect by enhancing release of substance P from unmyelinated C nerve fibres [Rains and Bryson, 1995]. It is modestly better than placebo in reducing the pain of knee OA and can take some weeks to take effect [Deal *et al.* 1991]. Again, local irritation may occur.

Glucosamine and chondroitin. Glucosamine (an aminosugar) and chondroitin sulphate (a glycosaminoglycan) are widely used for the treatment of OA, although their mechanisms of action are unclear. These are naturally occurring constituents of articular cartilage proteoglycans. A recent updated Cochrane review of glucosamine therapy in knee OA found pain and function improved by 28% and 21% in the Lesquene index, respectively, compared to placebo [Towheed *et al.* 2005]. The Lesquene index is a 10-question survey for patients with knee OA, assessing pain, walking distance, and activities of daily living, on a 0–24 scale [Dawson *et al.* 2005]. No improvement in WOMAC pain and function subscales were found. A lack of standardization in glucosamine preparations has contributed to the inconsistency in study results. The recent US NIH (National Institutes of Health) sponsored GAIT (Glucosamine/chondroitin Arthritis Intervention Trial) study found that the combination of glucosamine hydrochloride and chondroitin sulphate was only more effective than placebo in the subgroup with moderate-to-severe OA [Clegg *et al.* 2006]. In all other groups, response was similar. However, the study results are difficult to interpret in view of the high placebo response, patient selection, and the use of glucosamine hydrochloride. It is unclear if the latter has the same potential clinical benefits as glucosamine sulphate, because most studies showing efficacy for glucosamine in OA have used glucosamine sulphate. The effect size for trials which used glucosamine sulphate was 0.44 (95% CI 0.18–0.70) compared with 0.06 (95% CI 0.08–0.20) for those that used glucosamine hydrochloride [Zhang *et al.* 2008].

A 2003 meta-analysis evaluating chondroitin sulphate for knee OA found that the agent was significantly more effective for pain relief compared to placebo (ES = 0.43; 95% CI 0.32–0.54) [Richy *et al.* 2003]. No dose effect was noted, with 1200 and 800 mg/day being similarly effective. However, in the most recent systematic review, this was less clear. The ES for pain relief was large (ES = 0.74; 95% CI 0.50–0.99) but there was marked heterogeneity between trials [Reichenbach *et al.* 2007]. Whilst the data for glucosamine sulphate and chondroitin sulphate are conflicting, both agents are safe and well-tolerated. Hence, it is appropriate to trial both glucosamine sulphate and chondroitin sulphate to assess response, and patients should be urged to continue for at least 3 months as these medications are slow-acting.

Intra-articular therapy. The pain and secondary inflammation of knee OA can be effectively relieved by intra-articular corticosteroid injections at 1–3 weeks (ES = 0.72; 95% CI: 0.42–1.02), with a NNT of 4 [Bellamy *et al.* 2006]. Data for long-term efficacy and improvement in function are lacking. Good evidence for intra-articular corticosteroid injections in hip OA is sparse but the most recent RCT showed improvements in pain and mobility in the steroid-treated group (ES = 0.6) [Qvistgaard *et al.* 2006]. The long-term safety of steroid injections has been supported in a 2-year study [Raynauld *et al.* 2003]. No serious adverse events were also reported in the systematic review [Bellamy *et al.* 2006]. Attempts to identify predictors of response such as effusions have not been consistent. In addition, there have not been sufficient head-to-head studies comparing different steroid preparations. While it is not possible to predict individual patient responses, a trial of injections is certainly worthwhile as they are generally well-tolerated.

Hyaluronic acid is a large molecular weight glycosaminoglycan occurring in the synovial fluid of both normal and OA joints. The efficacy of viscosupplementation with hyaluronic acid injections in knee OA has been said to be comparable to NSAIDs and corticosteroid injections. A recent Cochrane review [Bellamy *et al.* 2005] concluded that hyaluronic acid showed superior efficacy compared to placebo for improvement in pain and function of knee OA. While no head-to-head analysis between specific products has been performed, viscosupplementation was more efficacious from 5 to 13 weeks with regard to pain, range of motion, and WOMAC and Lesquene scores [Hogenmiller and Lozada, 2006]. However, data on efficacy are inconsistent, and overall it probably has a small effect on pain relief [Bellamy *et al.* 2005]. Another meta-analysis in 2005 found no evidence for improved function and no effects on pain compared with saline injections. The inconsistent results have been attributed to inclusion of different controlled trials, differences in outcome measures and different statistical methods for data synthesis [Zhang *et al.* 2008]. The evidence for hip OA is much less. Acute local reactions have been reported in 2–8% postinjection.

Opioid analgesia. A recent meta-analysis demonstrated a moderate ES for pain reduction in OA (ES = 0.78; 95% CI 0.59–0.98) with median trial duration of 12 weeks [Zhang *et al.* 2008]. However, there was substantial heterogeneity between studies [Zhang *et al.* 2008]. Opioids are also associated with frequent adverse events, and the number needed to harm was 5 compared to placebo. The withdrawal rates were higher for stronger opioids (morphine, oxycodone) compared to weaker opioids (tramadol, codeine). There are also no long-term trials of opioids in OA. Nevertheless, they have an important role, with caution, in the management of patients with chronic, intractable pain for whom surgery is not an option and where other modalities have failed.

Other therapies. Diacerein: rhein, the active metabolite of diacerein, inhibits IL1 synthesis and activity which is implicated in cartilage destruction [Pelletier *et al.* 2006]. A meta-analysis of controlled clinical studies for knee and hip OA showed that diacerein was superior to placebo, similar to NSAIDS, and showed a carry-over effect at up to 2 months [Rintelen *et al.* 2006]. Further study is required before widespread use.

Complementary therapies: a number of complementary and alternative medications are being used extensively in the community to manage OA pain. These include S-adenosylmethionine (SAMe), methylsulfonyl-methane (MSM), dimethyl sulfoxide (DMSO) and green-lipped mussel (GLM). Unfortunately, there has been a paucity of good quality RCTs. A systematic review on DMSO and MSM highlighted significant methodological issues and the need for definitive efficacy trials [Brien *et al.* 2008a]. In the systematic review of GLM in OA, there were only four RCTs, and three were placebo-controlled. All assessed GLM as adjunctive therapy to conventional therapy. The findings of two studies could not be included because of methodological issues, and further rigorous studies are required [Brien *et al.* 2008b].

Disease/structure-modifying therapy
This is an area of active research at present. Table 1 lists agents that have been assessed for structure-modifying potential. All these trials have used radiological joint space narrowing or width as the structural outcome measure. There is now growing acceptance that x-rays are less sensitive that MRIs for measuring cartilage loss over time. Newer MRI imaging techniques, particularly compositional imaging such as

Table 1. Drugs assessed for disease-modifying potential in OA.

Agents	Proposed mechanisms of action	Observed structure-modifying effect
Glucosamine sulphate	May stimulate proteoglycan synthesis by chondrocytes, mild anti-inflammatory properties [McAlindon, 2006]	Lower x-ray progression in knee OA at 3 years [Hogenmiller and Lozada, 2006; Pelletier et al. 2006]
Chondroitin sulphate	Stimulates RNA synthesis by chondrocytes, partially inhibits leukocyte elastase, overcomes dietary deficiency of sulphur-containing amino acids [McAlindon, 2006]	Lower x-ray progression in knee OA at 2 years [Hogenmiller and Lozada, 2006; Pelletier et al. 2006]
Doxycycline	Inhibits matrix metalloproteases [Pelletier et al. 2006]	Lower x-ray progression in ipsilateral knee OA at 2.5 years [Hogenmiller and Lozada, 2006; Pelletier et al. 2006]
Diacerein	Inhibits IL-1 synthesis and activity	Lower x-ray progression in hip OA at 3 years [Pelletier et al. 2006]
Risedronate	Reduces bone marrow lesions in subchondral bone	No difference in knee OA at 2 years [Bingham et al. 2006]
Hyaluronic acid (HA)	Promotes endogenous HA production, anti-oxidant function in joints, ?lubricate the joint [Bagga et al. 2006; McAlindon, 2006]	No difference in knee OA at 1 year (less progression in milder disease) [Pelletier et al. 2006]
Avocado/soybean unsaponifiables	Repress chondrocyte catabolic activities, inhibit inflammatory mediators [Verbruggen, 2006]	No difference in hip OA at 2 years (less progression in severe disease) [Verbruggen, 2006]
Strontium ranelate	Stimulate the synthesis of type II collagen and proteoglycan [Bruyere et al. 2008]	May reduce x-ray progression of spinal OA [Bruyere et al. 2008]

dGEMRIC, T2 mapping and T1rho over the potential to detect early cartilage change before radiographic joint space narrowing becomes evident [Gray et al. 2008; Guermazi et al. 2008]. In addition, other structures within the knee joint such as subchondral bone, bone marrow lesions, meniscus and synovium should also be assessed as these may be relevant in the incidence and progression of OA.

Glucosamine and chondroitin sulphate are currently commonly used for symptom relief in OA. In a landmark clinical trial assessing the disease-modifying potential of glucosamine sulphate, patients were randomly assigned 1500 mg daily of glucosamine or placebo for 3 years [Pelletier et al. 2006]. Patients on placebo had progressive joint space narrowing whereas no significant joint space loss was seen in patients on glucosamine. These findings were corroborated by two other studies. However, the results have since been questioned because of the radiographic technique used to measure joint space width (JSW). The pooled results of two RCTs showed an ES of 0.24 for joint space loss reduction (95% CI 0.04–0.43). Radiological outcomes were assessed in the GAIT study using plain x-rays. There was no statistically significant difference in mean JSW loss observed in any treatment group (glucosamine hydrochloride;

chondroitin sulphate; glucosamine hydrochloride + chondroitin sulphate) compared to placebo. A trend was noted in Kellgren–Lawrence grade 2 knees towards improvement compared to placebo. The limitations of the study included limited sample size, variance of JSW measurement, and a smaller than expected loss in JSW [Sawitzke et al. 2008].

A few RCTs have reported favourable results for chondroitin sulphate as a DMOAD for knee OA. The most recent assessed radiographic progression at 2 years and revealed a significant decrease in JSW in the placebo group with no change in the chondroitin group (800 mg/day) [Pelletier et al. 2006].

Both doxycycline and diacerein have been assessed in double-blind RCTs. Diacerein was assessed in hip OA in a placebo-controlled RCT, and demonstrated significantly lower joint space narrowing in the active arm [Dougados et al. 2001]. However, similar effects were not seen in the knee OA study [Pham et al. 2004b]. Doxycycline, assessed in knee OA, showed less progression in the active arm compared to placebo. It is to be noted that this benefit was only observed in the study knee and not the contralateral knee. Interestingly, in the doxycycline study, there was a discord between

symptomatic and structural outcomes, possibly indicative of different pathways being responsible for these outcomes [Dougados *et al.* 2001]. However, this may have also been due to the selection of the study population, who were not uniformly seeking medical care for OA. Although there have been promising results in the search for DMOADs, questions of clinical significance remain and further studies are warranted.

New targets under evaluation

As highlighted earlier, OA is disease of the whole joint, and a number of tissue targets may be responsible for symptom (pain, function) and structure outcomes (radiological/MRI progression). A number of agents are being assessed in clinical trials. Calcitonin has shown promise via its potential effect on bone remodelling [Manicourt *et al.* 2006]. Vitamin D deficiency has been demonstrated to be a risk factor for OA, and studies are underway assessing Vitamin D replacement therapy on the development and progression of disease [Harvey and Hunter, 2008]. Cathepsin K and aggrecanase are capable of articular cartilage degradation [Hunter and Hellio Le Graverand-Gastineau, 2008]. ADAMTS5 is the major aggrecanase responsible for aggrecan degradation in murine OA. Inhibition of this protease is under clinical investigation [Hunter and Hellio Le Graverand-Gastineau, 2008].

Synovitis, frequently present in OA, may be mediated by interleukin (IL)-1B and tumour necrosis factor (TNF)-α. To date, IL-1 and TNF blockers have shown little success in OA clinical trials. A recent study of intra-articular anakinra found no improvement in symptoms compared to placebo in OA of the knee [Chevalier *et al.* 2009]. In another study of an autologous IL-1 antagonist, there was no difference compared to placebo with WOMAC outcomes [Yang *et al.* 2008]. However, these cytokines also enhance the release of prostaglandin E_2, inducible nitric oxide synthase (iNOS), and histamine from chondrocytes, meniscal cells and mast cells [Hunter and Hellio Le Graverand-Gastineau, 2008]. Animal models of arthritis and pain suggest that inducible Nitric Oxide Synthase (iNOS) inhibitors may have a role in OA treatment [Hunter and Hellio Le Graverand-Gastineau, 2008]. This was borne out in a recent study of inflammatory mediators produced by OA cartilage as detected by protein antibody array [Jarvinen *et al.* 2008]. Bradykinin,

released in synovitis, is able to excite and sensitize sensory nerve fibres. A recent phase II study demonstrated improvement in OA knee pain with a specific bradykinin-B_2 receptor antagonist compared to placebo [Hunter and Hellio Le Graverand-Gastineau, 2008].

Nerve growth factor (NGF) is another target of interest. NGF and its receptors are expressed in a number of joint tissues and are suggested to be involved in joint physiology and OA. Tanezumab, a humanized monoclonal antibody against NGF, was shown in two RCTs of chronic OA pain to significantly improve WOMAC scores more than placebo [Hunter and Hellio Le Graverand-Gastineau, 2008]. With the improved understanding of the pathophysiology of OA, the future is promising for the development of effective symptomatic and structure modifying agents.

Surgery

Surgery is indicated for patients with pain and impairment of function refractory to nonmedical and medical therapy. Joint replacement surgery results in improved pain and function, and is cost-effective in its capacity to improve quality of life [Lonner, 2003]. For hip and knee OA, total arthroplasty remains the definitive procedure. Given the nature of the intervention, most evidence stems from uncontrolled observational studies and cohort studies. A recent systematic review reported substantial improvements in pain and physical functioning [Ethgen *et al.* 2004]. Pain scores improved over 3–6 months. Minimally invasive arthroplasty is also available, with reported benefits including shorter hospital admission, and reduced need for narcotic analgesia and walking assisted devices at 2 weeks [Leopold, 2009]. However, there are only a few randomized trials and the technique is greatly dependent on the expertise of the surgeon [Leopold, 2009].

Unicompartmental knee arthroplasty is also being increasingly performed with faster recovery time [Lonner, 2003]. A recent systematic review showed similar outcomes with knee pain and function at 5 years after unicompartmental or total knee arthroplasty, with better range of movement after unicompartmental knee arthroplasty. Complication rates were similar but prosthesis survival was longer at 10 years for total knee arthroplasty (>90% compared to 85–90%) [Griffin *et al.* 2007].

Both shoulder and elbow replacements are also performed, albeit with less success than in the hip and knee. However, a recent large retrospective cohort study demonstrated that shoulder arthroplasties were as safe as the more commonly performed hip and knee arthroplasties [Farmer *et al.* 2007]. The shoulder arthroplasty group was noted to have a significantly lower comorbidity index than the knee arthroplasty group. Several surgical options are available for carpometacarpal joint OA.

When medical options are ineffective in managing OA, the willingness of the patient to consider surgery should be assessed along with comorbidities or modifiable risk factors that may prevent surgery. The optimal timing of joint replacement is also a key issue [Weng and Fitzgerald, 2006]. Long-term survival of the prosthesis is the major concern in the younger patient (<60 years old). It is hoped that improvement in prosthetic design and materials will lead to longer survival. Ninety-day postoperative outcomes after primary knee replacement have been described, and the following rates of complications have been observed: mortality (0.7%), readmission (0.9%), pulmonary embolus (0.8%), wound infection (0.4%) [Weng and Fitzgerald, 2006].

Arthroscopy with or without debridement is ineffective in OA of the knee unless there are loose bodies or meniscal tears needing removal or repair [Lonner, 2003]. The data for joint lavage and arthroscopic debridement in knee OA is limited, and largely consists of uncontrolled cohorts [Zhang *et al.* 2008]. A good placebo-controlled RCT with sham surgery demonstrated no significant differences in pain and function. However, methodological issues regarding study design and data analysis were raised regarding this study. A recent Cochrane review determined that arthroscopic debridement had no benefit for undiscriminated knee OA [Laupattarakasem *et al.* 2008]. In a recent RCT, arthroscopic surgery for OA of the knee was found to provide no additional benefit to optimized physical and medical therapy [Kirkley *et al.* 2008].

High tibial osteotomy (HTO) for medial compartment knee OA may delay the need for arthroplasty. This was assessed in a meta-analysis of 19 uncontrolled cohort studies, and good or excellent outcomes were achieved in 75% of patients at 60 months, and the average time to arthroplasty was 6 years [Zhang *et al.* 2008]. A Cochrane review found that valgus HTO improves knee function and improves pain [Brouwer *et al.* 2007]. Procedures such as drilling and abrasion arthroplasty are not always effective for managing articular cartilage defects [Wasiak *et al.* 2006]. When they are, long-term benefits may not be maintained and OA may develop, resulting in the need for total knee arthroplasty. Mosaicplasty and autologous cartilage implantation have also been used to manage focal chondral defects [Wasiak *et al.* 2006]. This is an area of ongoing research and better techniques are likely to be identified in the future. Lastly, joint fusion can be considered as a salvage procedure when joint replacement has failed [Zhang *et al.* 2008].

Conclusion

In summary, in patients identified with OA, conservative management options should be implemented including a combination of education, exercise and physiotherapy, weight loss, simple analgesia and neutraceuticals. There are promising early data for some disease modifying drugs but further studies are required. Functional aids and orthotics may also be indicated. As symptoms escalate, strategies including anti-inflammatories and intra-articular steroids can be employed. In a patient who continues to have pain, loss of function and/or disability despite optimal conservative management, surgery should be considered.

Conflict of interest statement

References

Bagga, H., Burkhardt, D., Sambrook, P. and March, L. (2006) Longterm effects of intraarticular hyaluronan on synovial fluid in osteoarthritis of the knee. *J Rheumatol* 33: 946–950.

Bagge, E., Bjelle, A., Eden, S. and Svanborg, A. (1991) Factors associated with radiographic osteoarthritis: results from the population study 70-year-old people in Goteborg. *J Rheumatol* 18: 1218–1222.

Bannwarth, B. (2006) Acetaminophen or NSAIDs for the treatment of osteoarthritis. *Best Pract Res Clin Rheumatol* 20: 117–129.

Barnsley, L. (2005) How to treat: osteoarthritis. *Australian Doctor* 18 March: 27–34.

Bellamy, N., Campbell, J., Robinson, V., Gee, T., Bourne, R. and Wells, G. (2005) Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev* CD005321.

Bellamy, N., Campbell, J., Robinson, V., Gee, T., Bourne, R. and Wells, G. (2006) Intraarticular corti-costeroid for treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev* CD005328.

Bingham III, C.O., Buckland-Wright, J.C., Garnero, P., Cohen, S.B., Dougados, M., Adami, S. *et al.* (2006) Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment osteoarthritis of the knee: results of the two-year multinational knee osteoarthritis structural arthritis study. *Arthritis Rheum* 54: 3494–3507.

Biswal, S., Medhi, B. and Pandhi, P. (2006) Longterm efficacy of topical nonsteroidal antiinflammatory drugs in knee osteoarthritis: metaanalysis of randomized placebo controlled clinical trials. *J Rheumatol* 33: 1841–1844.

Brien, S., Prescott, P., Bashir, N., Lewith, H. and Lewith, G. (2008a) Systematic review of the nutri-tional supplements dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM) in the treatment of osteoarthritis. *Osteoarthritis Cartilage* 16: 1277–1288.

Brien, S., Prescott, P., Coghlan, B., Bashir, N. and Lewith, G. (2008b) Systematic review of the nutri-tional supplement Perna Canaliculus (green-lipped mussel) in the treatment of osteoarthritis. *QJM* 101: 167–179.

Brouwer, R.W., Raaij van, T.M., Bierma-Zeinstra, S.M., Verhagen, A.P., Jakma, T.S. and Verhaar, J.A. (2007) Osteotomy for treating knee osteoarthritis. *Cochrane Database Syst Rev* CD004019.

Bruyere, O., Delferriere, D., Roux, C., Wark, J.D., Spector, T., Devogelaer, J.P. *et al.* (2008) Effects of strontium ranelate on spinal osteoarthritis progression. *Ann Rheum Dis* 67: 335–339.

Chevalier, X., Goupille, P., Beaulieu, A.D., Burch, F.X., Bensen, W.G., Conrozier, T. *et al.* (2009) Intraarticular injection of anakinra in osteoarthritis of the knee: a multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 61: 344–352.

Christensen, R., Astrup, A. and Bliddal, H. (2005) Weight loss: the treatment of choice for knee osteoar-thritis? A randomized trial. *Osteoarthritis Cartilage* 13: 20–27.

Cicuttini, F.M., Baker, J.R. and Spector, T.D. (1996) The association of obesity with osteoarthritis of the

hand and knee in women: a twin study. *J Rheumatol* 23: 1221–1226.

Cicuttini, F.M., Spector, T. and Baker, J. (1997) Risk factors for osteoarthritis in the tibiofemoral and patellofemoral joints of the knee. *J Rheumatol* 24: 1164–1167.

Clegg, D.O., Reda, D.J., Harris, C.L., Klein, M.A., O'Dell, J.R., Hooper, M.M. *et al.* (2006) Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med* 354: 795–808.

Cohen, J. (1988) Statistical power for the behavioral sciences (2nd ed.). The Effect size, Erlbaum: Hillsdale, NJ, pp. 8–14.

Dawson, J., Linsell, L., Doll, H., Zondervan, K., Rose, P., Carr, A. *et al.* (2005) Assessment of the Lequesne index of severity for osteoarthritis of the hip in an elderly population. *Osteoarthritis Cartilage* 13: 854–860.

Deal, C.L., Schnitzer, T.J., Lipstein, E., Seibold, J.R., Stevens, R.M., Levy, M.D. *et al.* (1991) Treatment of arthritis with topical capsaicin: a double-blind trial. *Clin Ther* 13: 383–395.

Dougados, M., Nguyen, M., Berdah, L., Mazieres, B., Vignon, E. and Lequesne, M. (2001) Evaluation of the structure-modifying effects of diacerein in hip osteoarthritis: ECHODIAH, a three-year, placebo-controlled trial. Evaluation of the Chondromodulating Effect of Diacerein in OA of the Hip. *Arthritis Rheum* 44: 2539–2547.

Ethgen, O., Bruyere, O., Richy, F., Dardennes, C. and Reginster, J.Y. (2004) Health-related quality of life in total hip and total knee arthroplasty. A qualitative and systematic review of the literature. *J Bone Joint Surg Am* 86-A: 963–974.

Farmer, K.W., Hammond, J.W., Queale, W.S., Keyurapan, E. and McFarland, E.G. (2007) Shoulder arthroplasty versus hip and knee arthroplasties: a comparison of outcomes. *Clin Orthop Relat Res* 455: 183–189.

Felson, D.T. (2004) An update on the pathogenesis and epidemiology of osteoarthritis. *Radiol Clin North Am* 42: 1–9, v.

Felson, D.T. (2006) Clinical practice. Osteoarthritis of the knee. *N Engl J Med* 354: 841–848.

Felson, D.T. (2009) Developments in the clinical understanding of osteoarthritis. *Arthritis Res Ther* 11: 203.

Felson, D.T., Anderson, J.J., Naimark, A., Walker, A.M. and Meenan, R.F. (1988) Obesity and knee osteoarthritis. The Framingham Study. *Ann Intern Med* 109: 18–24.

Felson, D.T., Zhang, Y., Anthony, J.M., Naimark, A. and Anderson, J.J. (1992) Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study. *Ann Intern Med* 116: 535–539.

Felson, D.T., Zhang, Y., Hannan, M.T., Naimark, A., Weissman, B., Aliabadi, P. *et al.* (1997) Risk factors for incident radiographic knee osteoarthritis in the elderly: the Framingham Study. *Arthritis Rheum* 40: 728–733.

Fransen, M. and McConnell, S. (2008) Exercise for osteoarthritis of the knee. *Cochrane Database Syst Rev* Oct 8(4): CD004376, Review.

Furukawa, T.A. (1999) From effect size into number needed to treat. *Lancet* 353: 1680.

Gray, M.L., Burstein, D., Kim, Y.J. and Maroudas, A. (2008) 2007 Elizabeth Winston Lanier Award Winner. Magnetic resonance imaging of cartilage glycosaminoglycan: basic principles, imaging technique, and clinical applications. *J Orthop Res* 26: 281–291.

Griffin, T., Rowden, N., Morgan, D., Atkinson, R., Woodruff, P. and Maddern, G. (2007) Unicompartmental knee arthroplasty for the treatment of unicompartmental osteoarthritis: a systematic study. *ANZ J Surg* 77: 214–221.

Guermazi, A., Burstein, D., Conaghan, P., Eckstein, F., Hellio Le Graverand-Gastineau, M.P., Keen, H. *et al.* (2008) Imaging in osteoarthritis. *Rheum Dis Clin North Am* 34: 645–687.

Hart, D.J., Doyle, D.V. and Spector, T.D. (1999) Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women: the Chingford Study. *Arthritis Rheum* 42: 17–24.

Harvey, W.F. and Hunter, D.J. (2008) The role of analgesics and intra-articular injections in disease management. *Rheum Dis Clin North Am* 34: 777–788.

Hinman, R.S. and Bennell, K.L. (2009) Advances in insoles and shoes for knee osteoarthritis. *Curr Opin Rheumatol* 21: 164–170.

Hogenmiller, M.S. and Lozada, C.J. (2006) An update on osteoarthritis therapeutics. *Curr Opin Rheumatol* 18: 256–260.

Hooper, L., Brown, T.J., Elliott, R., Payne, K., Roberts, C. and Symmons, D. (2004) The effectiveness of five strategies for the prevention of gastrointestinal toxicity induced by non-steroidal anti-inflammatory drugs: systematic review. *BMJ* 329: 948.

Hunter, D.J. and Hellio Le Graverand-Gastineau, M.P. (2008) How close are we to having structure-modifying drugs available? *Rheum Dis Clin North Am* 34: 789–802.

Jarvinen, K., Vuolteenaho, K., Nieminen, R., Moilanen, T., Knowles, R.G. and Moilanen, E. (2008) Selective iNOS inhibitor 1400W enhances anti-catabolic IL-10 and reduces destructive MMP-10 in OA cartilage. Survey of the effects of 1400W on inflammatory mediators produced by OA cartilage as detected by protein antibody array. *Clin Exp Rheumatol* 26: 275–282.

Jordan, K.M., Arden, N.K., Doherty, M., Bannwarth, B., Bijlsma, J.W., Dieppe, P. *et al.* (2003) EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis* 62: 1145–1155.

Kirkley, A., Birmingham, T.B., Litchfield, R.B., Giffin, J.R., Willits, K.R., Wong, C.J. *et al.* (2008) A randomized trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 359: 1097–1107.

Laupattarakasem, W., Laopaiboon, M., Laupattarakasem, P. and Sumananont, C. (2008) Arthroscopic debridement for knee osteoarthritis. *Cochrane Database Syst Rev* CD005118.

Leopold, S.S. (2009) Minimally invasive total knee arthroplasty for osteoarthritis. *N Engl J Med* 360: 1749–1758.

Lin, J., Zhang, W., Jones, A. and Doherty, M. (2004) Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. *BMJ* 329: 324.

Loeser, R.F. (2006) Molecular mechanisms of cartilage destruction: mechanics, inflammatory mediators, and aging collide. *Arthritis Rheum* 54: 1357–1360.

Lonner, J.H. (2003) A 57-year-old man with osteoarthritis of the knee. *JAMA* 289: 1016–1025.

Manicourt, D.H., Azria, M., Mindeholm, L., Thonar, E.J. and Devogelaer, J.P. (2006) Oral salmon calcitonin reduces Lequesne's algofunctional index scores and decreases urinary and serum levels of biomarkers of joint metabolism in knee osteoarthritis. *Arthritis Rheum* 54: 3205–3211.

McAlindon, T.E. (2006) Nutraceuticals: do they work and when should we use them? *Best Pract Res Clin Rheumatol* 20: 99–115.

McGettigan, P. and Henry, D. (2006) Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* 296: 1633–1644.

Messier, S.P., Loeser, R.F., Miller, G.D., Morgan, T.M., Rejeski, W.J., Sevick, M.A. *et al.* (2004) Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. *Arthritis Rheum* 50: 1501–1510.

Murphy, L., Schwartz, T.A., Helmick, C.G., Renner, J.B., Tudor, G., Koch, G. *et al.* (2008) Lifetime risk of symptomatic knee osteoarthritis. *Arthritis Rheum* 59: 1207–1213.

Pelletier, J.P., Martel-Pelletier, J. and Raynauld, J.P. (2006) Most recent developments in strategies to reduce the progression of structural changes in osteoarthritis: today and tomorrow. *Arthritis Res Ther* 8: 206.

Pham, T., Maillefert, J.F., Hudry, C., Kieffert, P., Bourgeois, P., Lechevalier, D. *et al.* (2004a) Laterally elevated wedged insoles in the treatment of medial knee osteoarthritis. A two-year prospective

randomized controlled study. *Osteoarthritis Cartilage* 12: 46–55.

Pham, T., Le, H.A., Ravaud, P., Dieppe, P., Paolozzi, L. and Dougados, M. (2004b) Evaluation of the symptomatic and structural efficacy of a new hyaluronic acid compound, NRD101, in comparison with diacerein and placebo in a 1 year randomised controlled study in symptomatic knee osteoarthritis. *Ann Rheum Dis* 63: 1611–1617.

Poole, A.R. (2002) Can serum biomarker assays measure the progression of cartilage degeneration in osteoarthritis? *Arthritis Rheum* 46: 2549–2552.

Qvistgaard, E., Christensen, R., Torp-Pedersen, S. and Bliddal, H. (2006) Intra-articular treatment of hip osteoarthritis: a randomized trial of hyaluronic acid, corticosteroid, and isotonic saline. *Osteoarthritis Cartilage* 14: 163–170.

Rains, C. and Bryson, H.M. (1995) Topical capsaicin. A review of its pharmacological properties and therapeutic potential in post-herpetic neuralgia, diabetic neuropathy and osteoarthritis. *Drugs Aging* 7: 317–328.

Raynauld, J.P., Buckland-Wright, C., Ward, R., Choquette, D., Haraoui, B., Martel-Pelletier, J. *et al.* (2003) Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 48: 370–377.

Reichenbach, S., Sterchi, R., Scherer, M., Trelle, S., Burgi, E., Burgi, U. *et al.* (2007) Meta-analysis: chondroitin for osteoarthritis of the knee or hip. *Ann Intern Med* 146: 580–590.

Richy, F., Bruyere, O., Ethgen, O., Cucherat, M., Henrotin, Y. and Reginster, J.Y. (2003) Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis. *Arch Intern Med* 163: 1514–1522.

Rintelen, B., Neumann, K. and Leeb, B.F. (2006) A meta-analysis of controlled clinical studies with diacerein in the treatment of osteoarthritis. *Arch Intern Med* 166: 1899–1906.

Roddy, E. and Doherty, M. (2006) Changing life-styles and osteoarthritis: what is the evidence? *Best Pract Res Clin Rheumatol* 20: 81–97.

Sawitzke, A.D., Shi, H., Finco, M.F., Dunlop, D.D., Bingham, III C.O., Harris, C.L. *et al.* (2008) The effect of glucosamine and/or chondroitin sulfate on the progression of knee osteoarthritis: a report from the glucosamine/chondroitin arthritis intervention trial. *Arthritis Rheum* 58: 3183–3191.

Scharf, H.P., Mansmann, U., Streitberger, K., Witte, S., Kramer, J., Maier, C. *et al.* (2006) Acupuncture

and knee osteoarthritis: a three-armed randomized trial. *Ann Intern Med* 145: 12–20.

Towheed, T.E., Maxwell, L., Anastassiades, T.P., Shea, B., Houpt, J., Robinson, V. *et al.* (2005) Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev* CD002946.

Towheed, T.E., Maxwell, L., Judd, M.G., Catton, M., Hochberg, M.C. and Wells, G. (2006) Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev* CD004257.

Verbruggen, G. (2006) Chondroprotective drugs in degenerative joint diseases. *Rheumatology (Oxford)* 45: 129–138.

Wasiak, J., Clar, C. and Villanueva, E. (2006) Autologous cartilage implantation for full thickness articular cartilage defects of the knee. *Cochrane Database Syst Rev* 3: CD003323.

Weng, H.H. and Fitzgerald, J. (2006) Current issues in joint replacement surgery. *Curr Opin Rheumatol* 18: 163–169.

White, A., Foster, N.E., Cummings, M. and Barlas, P. (2007) Acupuncture treatment for chronic knee pain: a systematic review. *Rheumatology (Oxford)* 46: 384–390.

Woolf, A.D. and Pfleger, B. (2003) Burden of major musculoskeletal conditions. *Bull World Health Organ* 81: 646–656.

Yang, K.G., Raijmakers, N.J., van Arkel, E.R., Caron, J.J., Rijk, P.C., Willems, W.J. *et al.* (2008) Autologous interleukin-1 receptor antagonist improves function and symptoms in osteoarthritis when compared to placebo in a prospective randomized controlled trial. *Osteoarthritis Cartilage* 16: 498–505.

Zhang, W., Jones, A. and Doherty, M. (2004) Does paracetamol (acetaminophen) reduce the pain of osteoarthritis? A meta-analysis of randomised controlled trials. *Ann Rheum Dis* 63: 901–907.

Zhang, W., Doherty, M., Arden, N., Bannwarth, B., Bijlsma, J., Gunther, K.P. *et al.* (2005) EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 64: 669–681.

Zhang, W., Moskowitz, R.W., Nuki, G., Abramson, S., Altman, R.D., Arden, N. *et al.* (2008) OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 16: 137–162.