Osteoarthritis: NSAIDs, paracetamol or other treatment approaches?

RICHARD O. DAY MD, FRACP **MARLENE FRANSEN** PhD, MPH
Series Editors **JANE ZOCHLING** MB BS, FRACP, MMed(ClinEpi), PhD
LYN MARCH MB BS, MSc, PhD, FRACP, FAFPHM

There is a strong evidence base to support the effectiveness of both nonpharmacological and pharmacological therapies for osteoarthritis.

Case study

A 56-year-old, fit, professional man presents with pain in his right knee, which has been increasing in intensity over the past year. He has led an active sporting life, playing squash as a younger man and more recently tennis. He had a few 'knee injuries' playing rugby but got over these quickly without surgery. He has always jogged but had to give this up one year ago because of the pain in his knees. He has noticed pain at night, which has woken him two or three nights a week over the past two months. He finds that after a session at the gym he has more pain and his right knee seems swollen.

On examination he was of an ideal bodyweight with a varus deformity of the right knee, obvious quadriceps wasting on the right, a small effusion of the knee joint, a 5° fixed flexion deformity, loss of 5 to 10° of flexion and crepitus on passive movement, most notable over the medial side of the joint (Figure 1). There was no ligamentous laxity. There was eversion of his right foot at the ankle and subtalar joints with loss of most of its transverse and longitudinal arches and with callus formation under the second and third metatarsophalangeal joints. There were signs of asymmetrical wear over the medial side of the sole of his right shoe.

AP and lateral weight-bearing x-rays of his knees revealed articular cartilage loss in the medial but also patellofemoral compartments of the right knee (Figure 2).

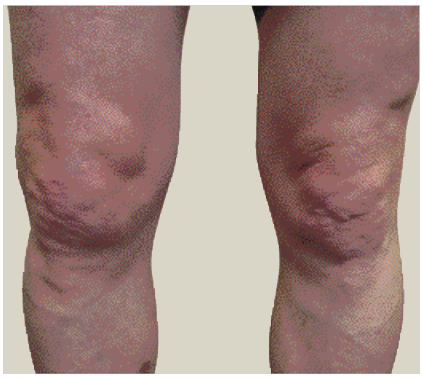

Figure 1. Patient with varus deformity due to osteoarthritis of the medial compartment of the right knee.

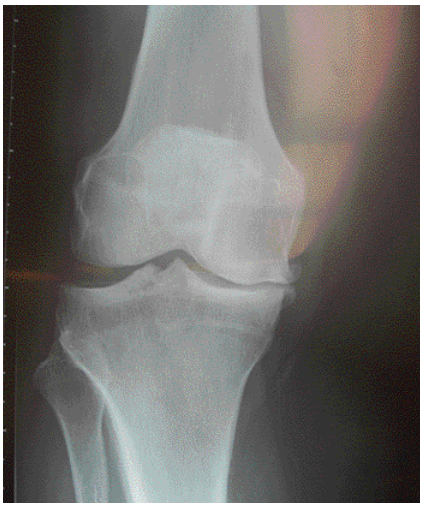

Figure 2. Weight-bearing x-ray of the right knee showing medial compartment cartilage loss and osteophytes.
PHOTOS COURTESY OF DR TOM CROSS

Case discussion

Pathophysiology

Osteoarthritis is prevalent and is a major contributor to disability in the adult population. As the population ages the incidence of osteoarthritis will increase. The most disabling forms involve weight-bearing joints of the hip and knee. The pathophysiology is complex and a number of biomechanical abnormalities, genetic factors and biochemical lesions leading to focal loss of articular cartilage have been identified.

A poor mechanical environment for the hip and knee joints includes excessive bodyweight, repetitive occupational lifting and bending, joint incongruency (e.g. joint dysplasia and postmenisectomy), joint instability (e.g. injury to ligaments and poor muscle control) and malalignment (often initiated by mechanical foot conditions or poor footwear).

Biochemical lesions include excessive break down by enzymes targeting articular cartilage constituents, namely collagen and/or hyaluranon ground substance,

Professor Day is a Rheumatologist and Clinical Pharmacologist at St Vincent's Hospital and University of New South Wales, Sydney. Dr Fransen is a Senior Research Fellow, Musculoskeletal Division at The George Institute for International Health, Sydney, NSW. Series Editors: Dr Zochling is a Research Fellow, Menzies Research Institute, University of Tasmania, Hobart, Tas. Associate Professor March is President of the Australian Rheumatology Association, and also Associate Professor of Medicine at the University of Sydney, Department of Rheumatology at Royal North Shore Hospital, Sydney, NSW.

and also anabolic mechanisms resulting in insufficient synthesis of new articular cartilage. Ageing appears to make the cartilage more vulnerable to any of the above degenerative mechanisms.

Although not a primary mechanism of joint destruction, an inflammatory component has been identified in osteoarthritis. This is most likely due to intra-articular reactions to debris generated by the arthritic process and is thought to contribute to the stiffness and pain. The joint lesions can result in symptomatic osteoarthritis, which presents with joint pain, stiffness and loss of function. Characteristically there is bony enlargement of the joint in osteoarthritis and deformity as seen in the patient described above.

Signs and symptoms

The diagnosis of osteoarthritis is largely a clinical one based on the history and examination of the patient. There is a common form of osteoarthritis (nodal osteoarthritis) that strongly runs in families. This particularly affects the hands and is common in women who have first-degree female relatives similarly afflicted, indicating a strong genetic association.

The distribution of affected joints associated with osteoarthritis contrasts with rheumatoid arthritis in that the distal and proximal interphalangeal joints as well as the first carpometacarpal joints are affected symmetrically in osteoarthritis. On palpation of the osteoarthritic joints, it is apparent that the enlargement is boney in nature.

Stiffness associated with osteoarthritis has a characteristic pattern. It is sometimes described as an 'inactivity stiffness' as it manifests following periods of inactivity – for example, getting out of a car or a chair. This differs from inflammatory arthritides, such as rheumatoid arthritis, by which stiffness is experienced in the morning and its duration and intensity are related to the severity of the synovitis.

Other symptoms of osteoarthritis include locking of the knee and instances of the knee giving way. These symptoms are not typical of osteoarthritis and often indicate internal derangement such as mensical or cruciate ligament tears.

X-rays may reveal a loss of cartilage and in the hips and knees this is best demonstrated by weight-bearing x-rays. Osteophytes may present around the margins of the joint (Figure 2). Haematological and biochemical screening is unremarkable in osteoarthritis.

Approach to management

There is a strong evidence base to support the effectiveness of both nonpharmacological and pharmacological therapies for osteoarthritis.

Nonpharmacological therapies

Weight reduction, muscle strengthening and aerobic exercise

There is level 1 evidence for weight reduction, muscle strengthening around the affected joints and aerobic exercise to improve endurance and fitness in patients with osteoarthritis.

Supervision by a health professional is usually required at the initiation of a weight loss or exercise program for people with joint problems, with regular ongoing monitoring and encouragement for sustainability of effect.

Improving endurance and fitness not only help with the joint disease, but also reduce the risk of serious comorbidity associated with sedentary lifestyles.

Dietary manipulation and food supplements

Dietary manipulation is of great interest to patients with osteoarthritis and there is good evidence that symptomatic relief accrues in inflammatory arthritis from supplementation with fish oil (omega-3 fatty acids). This effect is attributed to a diet-induced change in the nature of prostaglandins, which contribute to inflammation. In osteoarthritis it is reasonable to infer that any inflammatory reaction contributing to the symptoms will be muted, but efficacy in osteoarthritis has not been proven.

Glucosamine sulfate introduced as a food supplement is now an over-the-counter or complementary medicine. The conflicting results for analgesic benefit from the many randomised clinical trials conducted to date has been attributed either to the influence of manufacturer sponsorship of the research, formulation variation between products, study methodological issues or the marked differences in the presence of obesity and structural disease severity among study participants between the clinical trials. The analgesic effect is seen in patients who are going to respond within one to two months and maintenance therapy is required. There is also contentious evidence that this treatment is disease modifying and can reduce the rate of cartilage loss. Large studies are underway examining this proposition.

Recent meta-analyses of trials investigating chondroitin sulfate have not confirmed initial studies that this product provided symptomatic benefit in patients with osteoarthritis.

There are many other dietary modifications that are enquired about by patients. For example, it is common for patients to ask about tomatoes and so called acidic foods, but there is no evidence for any useful effect of withdrawal of these foods from the diet in patients with osteoarthritis.

Pharmacological therapies

The pharmacological treatment of osteoarthritis at this stage remains symptomatic only and there is no evidence of disease modification by any registered medicine.

Paracetamol

There is good evidence that paracetamol taken in sufficient amounts is a reasonable analgesic in patients with mild-to-moderate osteoarthritis affecting weight-bearing joints, particularly the knees. Convincing patients of the value of trying paracetamol requires some effort as most have tried

continued

Table. Risks associated with NSAID toxicity

Risk factors for NSAID toxicity	Risk
Patient's age (>65 years)	GI ulcer, bleeding, perforation
Previous peptic ulcer	GI ulcer, bleeding, perforation
Previous gastrointestinal bleed	GI ulcer, bleeding, perforation
Renal impairment	Worse renal impairment
Cardiac failure	GI ulcer, bleeding, perforation and worse cardiac failure
Cardiovascular risk factors – obesity – hypertension – diabetes – hyperlipidaemia – smoking – unfit	Myocardial infarction (risk is low but increases with a high background risk) and loss of control of hypertension in patients with high blood pressure

occasional doses without success. A trial of regular and sufficient paracetamol (up to 4 g/day in otherwise well adults) is needed to exclude efficacy in an individual patient. The drug is remarkably safe with no proven detrimental effects on the gastrointestinal tract, cardiovascular system or kidneys when taken within the recommended dosage range. There have been a small number of epidemiological studies suggesting weak associations, with cardiovascular and renal disorders, but these results have not been verified by robust controlled clinical trials and the possibility of bias remains.

A modified-release paracetamol in a 665 mg dose (Panadol Osteo) is PBS listed for relief of persistent pain associated with osteoarthritis. This allows dosing to be decreased to eight hourly, which improves convenience for some patients.

NSAIDs

There is good evidence that NSAIDs are efficacious and slightly but significantly more efficacious than paracetamol for moderate-to-severe osteoarthritis.

Comparisons of NSAIDs, including selective COX-1 sparing agents, do not suggest that any one agent in this class has a substantive advantage over another. Generally, the doses required to provide benefit for osteoarthritis are less than those required in inflammatory conditions such as rheumatoid arthritis. (For example, typical doses for osteoarthritis would be diclofenac 25 to 50 mg twice daily, meloxicam [Meloxibell, Mobic, Movalis, Moxicam] 7.5 mg daily and naproxen 250 mg twice daily.) There is a tendency for the dosage to increase if the lower doses have not been as efficacious as wished. This tendency should be resisted because the incidence of adverse reactions increases with increasing dose, and increments in efficacy, if seen at all, are often not great.

There is justified concern about the risk of gastrointestinal adverse effects with NSAIDs notably peptic ulcers and complications of these. Bleeding from the large bowel caused by damage to the gastrointestinal mucosa is now known to be an adverse effect of NSAIDs. These effects are due to inhibition of mucosal prostaglandin synthesis (prostaglandins are protective in the gut) particularly against acid-induced damage. Strategies to reduce the risk of ulceration and bleeding include using COX-1 sparing agents (celecoxib [Celebrex], meloxicam) and/or using concomitant gastroprotective agents notably proton pump inhibitors.

In patients at higher risk of gastrointestinal ulceration and bleeding, particularly elderly patients and those with a prior history of ulceration, the use of proton pump inhibitors as well as less gastrotoxic NSAIDs is reasonable. The latter include celecoxib, meloxicam, ibuprofen and diclofenac. If at all possible and reasonable, it is best not to use these medicines at all in these high-risk patients.

The NSAIDs variably and in a dose-related manner can increase blood pressure, particularly in patients who are already hypertensive whether they are treated or not. Furthermore, renal function can be impaired and the adverse reaction is dose related and more likely to occur in patients with pre-existing renal impairment, which is common in the elderly (Table).

Rofecoxib (Vioxx) was withdrawn from the market because of an increased risk of myocardial infarction. It was clear that this was also a dose-related adverse reaction. The level of risk from the other COX-1 sparing agents remaining on the market, namely celecoxib and other NSAIDs such as meloxicam, naproxen, ibuprofen and diclofenac remains controversial.

Many studies suggest a low risk from NSAIDs expressed in terms of relative risk of the order of one- to twofold. The patient's background risk is also important: a relative risk of two on a very low background risk will raise few concerns. These risk rates are based largely on observational not randomised studies. However, patients at risk of myocardial infarction might be better managed without NSAIDs if at all possible.

All patients taking NSAIDs, particularly those who are older or have diabetes, should be advised to attend to their risk

factors to reduce their risk of myocardial infarction. For example, patients should have their blood pressure controlled and elevated plasma lipids lowered, those who smoke should stop, ideal bodyweight should be maintained and regular exercise undertaken, the latter if possible with osteoarthritis of weight-bearing joints.

NSAIDs and other agents such as capsaicin (Zostrix) can be delivered topically. These have proven efficacy but are less effective than orally administered NSAIDs. No comparative trials of topically applied NSAIDs have revealed significant superiority of one product over another. However, they can be beneficial for many patients and can be applied intermittently.

Combination therapy with paracetamol and NSAIDs

There is little data on the value of combinations of paracetamol and NSAIDs. However, it would seem rational to use a baseline regimen of regular and sufficient paracetamol and supplement this with NSAIDs only as or if needed. A good general rule with NSAIDs is to use the lowest dose for the shortest time to manage the symptoms, and preferably in combination with optimal nonpharmacological therapy.

Intra-articular and periarticular therapy

Intra-articular and periarticular therapy is helpful and efficacy has been achieved with periarticular and intra-articular depot-corticosteroid injections used judiciously and intermittently. Furthermore, hyaluranon intra-articular injections are efficacious to a variable degree in approximately 70% of patients with symptomatic osteoarthritis of the knees. However, the effects last on average for six months only and the therapy is expensive at over $400 to purchase a course of hyaluranon, which is injected weekly on three to five occasions depending on the product. These products are not supported by the PBS or RPBS because they have not been accepted as cost effective.

Conclusion

In conclusion, weight reduction (if overweight), graded exercise and paracetamol remain the mainstays of treatment for patients with osteoarthritis. These primary management strategies should be given a proper trial before being abandoned. NSAIDs are slightly more effective than paracetamol in moderate-to-severe osteoarthritis of the knee, but a proportion of these patients will find paracetamol effective most of the time. NSAIDs have particular toxicities, affecting the gastrointestinal tract and cardiovascular and renal systems, which need to be taken into account. MT

Further reading

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COMPETING INTERESTS: Professor Day has been an advisory board member for Vioxx (Merck Sharp & Dohme) and Celebrex (Pfizer) and remains on the advisory boards for over-the-counter Panadol (GlaxoSmithKline) and over-the-counter ibuprofen (Reckitt Benniser). Any recompense is placed in audited trust funds of St Vincent's Hospital, Sydney. Dr Fransen: None.