Osteoarthritis

I Haq, E Murphy, J Dacre

Osteoarthritis is a chronic degenerative disorder characterised by cartilage loss. It is extremely prevalent in society and is a major cause of disability. It is important to treat osteoarthritis effectively using a multidisciplinary approach tailored to the patient’s needs. This paper reviews current thinking on the aetiology, pathogenesis, investigations, and management of osteoarthritis. The paper also discusses the challenges for developing good quality outcome measures for use in large scale multicentre clinical trials for new osteoarthritis treatments, especially disease modifying osteoarthritis drugs.

Osteoarthritis is a chronic, degenerative disorder of unknown cause characterised by gradual loss of articular cartilage. It is the most prevalent disease in our society, with a worldwide distribution. It ranks fourth in health impact in women and eighth in men in the western world. In England and Wales, between 1.3 and 1.75 million people have symptomatic osteoarthritis. Data from the Arthritis Research Campaign show that up to 550 000 people in the UK have severe knee osteoarthritis and two million people visited their general practitioner in the past year because of osteoarthritis. More than 80 000 hip or knee replacements were performed in 2000 in the UK with a cost of £405 million. As a cause of disability (such as walking and stair climbing) in the elderly in the west, osteoarthritis is second only to cardiovascular disease. Altogether 10%–15% of adults over 60 have some degree of osteoarthritis, and with an ageing population it is becoming an increasingly important disease.

Osteoarthritis is classified into two groups. Primary osteoarthritis can be localised or generalised, the latter more commonly found in post-menopausal women, with development of Heberden’s nodes. Secondary osteoarthritis has an underlying cause, such as trauma, obesity, Paget’s disease, or inflammatory arthritis.

CLINICAL FEATURES

Patients are usually over the age of 50 and complain of pain and stiffness in the affected joint(s), which is exacerbated with activity and relieved by rest. Early morning stiffness, if present, is typically less than 30 minutes.

Joint tenderness and crepitus on movement may also be present. Swelling may be due to bony deformity such as osteophyte formation, or due to an effusion caused by synovial fluid accumulation. Systemic symptoms are absent, with a normal erythrocyte sedimentation rate. The presence of fever, weight loss, anorexia, or abnormal blood tests should alert the physician to other disease processes such as infection or malignancy.

The American College of Rheumatology have produced criteria for the diagnosis of osteoarthritis. They were developed for epidemiological purposes and are not recommended for use in routine clinical practice.

PATHOGENESIS

Traditionally, osteoarthritis was viewed as an inevitably progressive, degenerative disease process. New work suggests that it is a dynamic process that may progress episodically. It is a heterogeneous group of diseases characterised by an adaptive response of synovial joints to a variety of environmental, genetic, and biomechanical stresses.

Cartilage is made of water (70%) and a type II collagen framework with proteoglycans and glycosaminoglycans (consisting mainly of aggrecan and also chondroitin), produced by chondrocytes. Proteoglycans in turn bind to hyaluronate which stabilises the macromolecule. Chondrocytes receive nutrition from the synovium by diffusion and the synovial fluid is circulated by joint movement. It has been postulated that if the joint stops moving (as a result of a fracture or immobility) and chondrocytes lose their source of nutrition, they go into shock and cartilage repair ceases. Metalloproteinases are produced, which catalyse collagen and proteoglycan degradation. The synovium has been shown to be variably inflamed in osteoarthritis producing increased levels of interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF-α), cytokines that induce nitric oxide and metalloproteinase production. Interleukin-6 (IL-6) and mechanical loading of the joint also induce catabolic cytokine receptors. These bind IL-1 and TNF-α within cartilage causing more destruction.

It is thought that the osteophytes and subchondral sclerosis seen in osteoarthritis may be the body’s way of trying to compensate for lack of cartilage, although some researchers have found bony changes before cartilage changes in animal models. This sort of abnormal bone is also thought to lead to further degradation of the cartilage surrounding it. Poor synthesis of cartilage

See end of article for authors’ affiliations
Correspondence to: Dr Inam Haq, Academic Centre for Medical Education, 4th Floor Holborn Union Building, Archway Campus, Highgate Hill, London N19 3LW, UK
i.haq@acme.ucl.ac.uk
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Abbreviations: COMP, cartilage oligomeric matrix protein; COX-2, cyclo-oxygenase-2; IL-1/IL-6, interleukin-1/interleukin-6; NICE, National Institute for Clinical Excellence; NSAIDs, non-steroidal anti-inflammatory drugs; SF-36, short form 36; TNF-α, tumour necrosis factor-alpha; WOMAC, Western Ontario and McMaster Universities osteoarthritis index
osteoarthritis. It is reduced in an elderly patient group with knee osteophyte formation.

The normal ageing process is thought to cause increased laxity around joints, reduced joint proprioception, cartilage calcification, and reduced chondrocyte function, all leading to a propensity for osteoarthritis. The Framingham Study found that 27% of those aged 63 to 70 had radiographic evidence of knee osteoarthritis, increasing to 44% in the over 80 age group. Other studies have found that 80% of people over the age of 65 have some radiographic evidence of osteoarthritis (although this may be asymptomatic), but that incidence and prevalence of symptomatic osteoarthritis levelled off or declined in men and women at around 80 years of age.

Studies of proprioception in osteoarthritis have found that it is reduced in an elderly patient group with knee osteoarthritis.

PATHOLOGICAL FINDINGS
Macroscopically, the osteoarthritic process results in cystic degeneration of the bone surrounding the joint, with loss of cartilage and irregular, abnormal bone formation at the edges of the joint (osteophytes; fig 1) and narrowing of the joint space.

Microscopically, there is flaking and fibillation of the articular cartilage surface and destruction of the cartilage microarchitecture with formation of holes within it, as well as bony cysts. Variations in the cellularity and vascularity of subchondral bone leads to sclerosis in some areas and new bone and callous formation where the synovium is continuous with the periosteum. The cartilage itself has three discrete zones within it: a surface layer adjacent to the synovium consisting of collagen aligned parallel to the surface, a middle zone consisting of thicker, wider spaced collagen molecules arranged randomly, and an inner zone adjacent to bone, consisting of collagen arranged perpendicular to the surface.

RISK FACTORS
Age
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Trauma
Cruciate, collateral ligament and meniscal tears as well as joint fracture lead to increased risk of osteoarthritis. The Framingham Study found men with a history of knee injury were at a 5–6-fold increased risk of developing osteoarthritis. This usually occurs in a younger age group and can lead to prolonged disability and unemployment. Meniscectomy after a knee injury resulted in an increased risk of developing tibiofemoral osteoarthritis.

Occupation
Osteoarthritis is commoner in those performing heavy physical work, especially if this involves knee bending, squatting, or kneeling. Dockers and miners have been found to have a higher prevalence of knee osteoarthritis than those in sedentary jobs. There is a significant relationship between occupational kneeling or repetitive use of joints during work and osteoarthritis.

Exercise
Elite athletes who take part in high impact sports do have an increased risk of knee osteoarthritis. Primary quadriiceps weakness is a risk factor for its development by decreasing the stability of the joint and reducing the shock absorbing properties of the muscle.

Gender and ethnicity
Under the age of 50, men have a higher prevalence and incidence than women. However, once over 50, women have a higher overall prevalence and incidence than men. This difference tends to become less marked after the age of 80. A withdrawal from oestrogen at menopause may be a trigger.

Although ubiquitous, osteoarthritis is generally commoner in Europeans than in Asians. Osteoarthritis of the hip is more common in Europeans (7%–25%) than in Chinese, Africans from Nigeria and Liberia, and Jamaicans (1%–4%). Osteoarthritis of the hand is more common in European women than in women of Afro-Caribbean descent. There is conflicting evidence as to whether oestrogen based hormone replacement therapy protects against large joint osteoarthritis.

Genetics
There is increased concordance for osteoarthritis in monozygotic twins compared with dizygotic twins, indicating there is a genetic susceptibility to the disease.

Many genes have been linked to osteoarthritis. There is most concordance with chromosomes 2q, 4, and 16. Families have been found with rare autosomal dominant patterns of inheritance of osteoarthritis. The defective genes are often coding for structural proteins of the extracellular matrix of the joint and collagen proteins. Children of parents with early onset osteoarthritis are at higher risk of developing it themselves compared with families where this is not the case (reviewed in Loughlin).  

Obesity
This is the strongest modifiable risk factor. Three to six times the body weight is transferred across the knee joint during walking. Any increase in weight should be multiplied by this factor to estimate the excess force across the knee joint when an overweight patient walks. The Chingford Study showed that for every two unit increase in body mass index (approximately 5 kg), the odds ratio for developing radiographic knee osteoarthritis increased by 1.36. Increasing weight increased the risk of contralateral osteoarthritis of the knee in women with established osteoarthritis of one knee.

Being overweight at an average age of 36–37 is a risk factor for developing knee osteoarthritis in later life (>70 years of age). Losing 5 kg of weight reduced the risk of symptomatic knee osteoarthritis in women of average height by 50%. Also, increased risk of developing progressive osteoarthritis seems to be apparent in overweight people with localised disease.

Diet
People in the lower tertile of vitamin C and vitamin D blood levels had a threefold risk of progression of knee
osteoarthritis. The antioxidant and collagen promoting properties of vitamin C may be of benefit as animal models have shown vitamin C may delay the onset of osteoarthritis. Vitamin D intake and status had no effect on development of knee osteoarthritis but those with low intake and low serum levels had an increased risk of osteoarthritis knee progression. Vitamin E has not been shown to be of benefit.

Bone density

There is an inverse relationship between bone density and osteoarthritis. Increasing subchondral bone density may lead to increased loading through weightbearing joint cartilage.

Natural history

The natural history of osteoarthritis is a slow process:

In the knee, progression may take many years. Once established however, the joint may remain in a stable condition for many years. Spector et al found that in a cohort of 63 patients, radiographic deterioration occurred in approximately one third. In another study of 31 patients with established knee osteoarthritis followed up for eight years, 20 patients got worse and seven remained the same. Changes in symptoms, disability, and radiographs do not correlate.

In the hip, natural history is variable. In a Danish study, two thirds of hips studied deteriorated radiographically over 10 years, however symptomatic improvement was common. Other studies have shown clinical deterioration to be more common. Unlike knee osteoarthritis, symptomatic and radiological recovery is possible. Avascular necrosis of the femoral head occurs late in disease and is a major problem.

In the hand it is initially a relapsing and remitting disease with episodic inflammatory phases associated with joint redness and swelling. Bony swellings form at this time. The frequency of disease flares then reduces and the joint swellings become hard and fixed. This is associated with a reduction in pain.

Investigations

Imaging

Plain radiographs

The following changes may be seen on plain radiographs (fig 2):

- Joint space narrowing.
- Osteophytes.
- Bony cysts.
- Subchondral sclerosis.

Radiographs are cheap, provide a permanent record, and are easily available. They are not a good measure of disease progression as this is based on measures of joint space narrowing, which occurs at <0.1 mm per year, so it is difficult to measure accurately.

Scoring systems to quantify radiological progression

Several radiograph scoring systems have been employed to assist the measurement of osteoarthritis progression. Other techniques include chondrometry, where minimal interbone distance is measured using a special compass magnifying glass calibrated to 0.1 mm (reviewed in Hochberg). Dacre and Huskisson have developed a reliable computerised method for measuring total tibiofemoral compartment joint space. A digitised image of a standard anteroposterior knee radiograph is obtained and the area of the knee joint space is measured. Microfocal radiography allows magnification of the image (usually 4–10 times) with high spatial resolution, sharply defined joint margins, allowing accurate and reproducible measurements of radiographic features.

Relationship between radiography findings and symptoms

Results have been conflicting, probably due to the differences in populations studied and radiographic and clinical criteria used. The presence of osteophytes had a very strong association with knee pain, whereas the absence or presence of joint space narrowing was not associated. Knee pain severity was a more important determinant of functional impairment than radiographic severity of osteoarthritis. There was no correlation between joint space narrowing and a disability score (Western Ontario and McMaster Universities Osteoarthritis index, WOMAC) at a single time point.

Magnetic resonance imaging

This is already well established for use in assessing ligament and meniscal tears in the knee. It has no place in routine clinical assessment of osteoarthritis, but may be a specific and sensitive way of quantifying cartilage loss. Currently, magnetic resonance imaging has not proved to be sensitive enough in the detection of preclinical osteoarthritis. Changes in surface morphology and full thickness cartilage defects can be seen, but fibrillation cannot yet be evaluated.

Other imaging techniques

Computed tomography is thought to have little advantage over plain radiographs unless an axial joint view is required. Radionuclide imaging is considered inadequate in assessing disease progression as it lacks sufficient anatomical detail. However studies have found that retention of technetium labelled diphosphonate in the knee predicts subsequent cartilage loss in patients with advanced osteoarthritis. Thus far, radionuclide imaging has not been recommended as a routine imaging modality due to worries about radiation exposure. Ultrasound is good for assessing cartilage integrity and destruction, but in most weight bearing joints, cartilage is not easily accessible.

Biochemical markers in osteoarthritis

Current diagnosis of osteoarthritis relies on a clinical history and radiography. Radiographic changes occur late in the disease and are largely irreversible. Molecular markers may theoretically be able to detect osteoarthritic changes at an early stage. Ideally these markers would be sensitive to change, reliable, and quantitative.

There are currently several candidates for biochemical markers in osteoarthritis, but none have been found to be specific so far. They reflect remodelling of the bone, cartilage, and synovium.

Cartilage oligomeric matrix protein (COMP) may be a marker of cartilage destruction. C-reactive protein, hyaluronan, YKL-40, and metalloproteases are markers of synovial inflammation. Pyridinoline and bone sialoprotein are markers of bone turnover.
A major problem is that most of the body cartilage is found in intervertebral discs and costochondral junctions. Joints affected by osteoarthritis form a small proportion of the total by number and may develop only subtle biochemical changes in early disease.

These markers need to be validated as no single marker can yet distinguish between a healthy subject and an osteoarthritis patient on an individual basis. A recent study showed that a combination of three markers (TNF receptor II, COMP, and epitope 846) discriminated between healthy controls and affected by osteoarthritis form a small proportion of the total in intervertebral discs and costochondral junctions. Joints

**OUTCOME MEASURES TO BE USED IN CLINICAL TRIALS**

With current interest in the development of possible disease modifying osteoarthritis drugs, it is important to have suitable outcome measures that are sensitive to change in articular cartilage thickness, reproducible (precise), and accurate (valid). These outcome measures can then be used in large multicentre clinical trials to assess efficacy of new treatments. Ideally, these measures would reflect current disease activity, damage due to previous disease, and effect on health status.

Radiographic measurement of joint space width remains the method of choice for evaluation of efficacy of disease modifying drug. Brandt et al concluded that the current anteroposterior knee radiograph was unable to provide reproducible measurements of joint space narrowing and that its estimation depended on anatomical positioning of the knee.

Results from ongoing studies to assess progression of osteoarthritis using different knee positioning protocols will help in defining a gold standard method of assessment of joint space narrowing.

Any assessment of outcome in interventions in osteoarthritis needs to take into account a measure of impairment and quality of life. For lower limb osteoarthritis the most widely used measure is the WOMAC. General health questionnaires used include the short form 36 (SF-36) and health assessment questionnaire. These instruments are important for measuring clinically important changes in response to treatments, and are used in clinical trials. They may be difficult to use in routine clinical practice due to time pressures. The WOMAC is a measure of pain, stiffness, and physical functional ability. The SF-36 covers areas such as physical function, general health, and social and psychological function. The WOMAC and SF-36 have been shown to be valid and responsive in those on non-steroidal anti-inflammatory drug (NSAID) treatment. A recent study has shown that both WOMAC and SF-36 show improvements in pain scores in patients with hip or knee osteoarthritis undergoing an intensive physical therapy rehabilitation programme. The WOMAC was better at detecting functional improvement.

**MANAGEMENT OF OSTEOARTHRITIS IN CLINICAL PRACTICE**

The aims of management of patients with osteoarthritis are:

- Patient education.
- Pain control.
- Improve function.
- Alter the disease process.

Management interventions in osteoarthritis include:

- Education.
- Exercise.
- Weight loss.
- Physiotherapy.
- Appliances.
- Drugs.
- Surgery.

Each management plan should be individualised and patient centred, agreed on by the patient and doctor in a mutual discussion. Non-pharmacological measures should be tried first, and plans may need to be modified as the patient condition changes. The multidisciplinary team should also be involved.

**Non-drug therapy**

**Education and community support**

Walker-Bone et al performed a meta-analysis of 10 trials between 1989 and 1997 on patient education and outcome for pain and function. They concluded that there was a significant effect, but that it was only 20% as effective as NSAIDs. Formal education by any member of the multidisciplinary team should be an initial part of management.

**Exercise**

This is the single most important intervention. Inactivity due to the pain of osteoarthritis leads to reduction of muscle bulk surrounding the joint, thus destabilising it. Aerobic capacity is also reduced, and the risk of obesity is increased. Exercise is needed to build muscle strength and endurance, improve flexibility and joint motion, and improve aerobic activity.

There have been many studies showing the benefit of exercise in osteoarthritis. Evidence suggests that while advice regarding exercise is important, being given a specific programme to do with “follow up” is probably more effective than advice alone. Given improved outcomes in nearly all these trials in osteoarthritis and exercise, it is likely that compliance is good, although none seem to have measured it directly. Box 2 shows the American Geriatrics Society protocol for an exercise programme.

**Weight loss**

A study of 21 obese elderly men and women with knee osteoarthritis randomised to either a diet and exercise group or diet...
alone group found that the former group lost more weight but both groups had similar improvements in self reported disability, knee pain intensity, and frequency after six months.46

Mechanical aids
In knee osteoarthritis, shock absorbing footwear reduces the impact of a load on the knee. Heel wedging improves proprioception and reduces pain in osteoarthritis of the knee. The occupational therapist can provide assessment for walking aids, for example, sticks and for providing a safe and functional environment at home and work. There is historical and anecdotal evidence for their benefit rather than from controlled trials.

Drug therapies

Analgesics
Paracetamol is used first line up to a dose of 1 g four times a day. It is safe and well tolerated, especially in older age groups. Acetaminophen, combinations such as co-proxamol may be used if paracetamol alone is unhelpful. Stronger opiates should be avoided if at all possible. Both the American College of Rheumatology and European League Against Rheumatism guidelines recommend this as initial therapy.47 48

Non-steroidal anti-inflammatory drugs
NSAIDs have been found to have equal efficacy to paracetamol in most patients. There are no predictors of response to NSAIDs,49 and no evidence that NSAIDs are more effective in those patients with clinical signs of joint inflammation than in those with none. Interestingly there is also no evidence to confirm the widely held view that NSAIDs are superior to those with none. Interestingly there is also no evidence to confirm the widely held view that NSAIDs are superior to

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Intra-articular corticosteroids
There are significant short term benefits of 2–4 weeks over placebo with injection of triamcinolone hexafluoride or methylprednisolone in knee joints. Data on hip, thumb base, and finger injections are lacking. Anecdotal evidence suggests some patients achieve a sustained improvement in symptoms. Side effects include skin atrophy and dermal depigmentation, especially with long acting preparations and if the soft tissues are injected. Infection is an important but rare complication. Early studies suggested the possibility of severe cartilage destruction with excessive use. It seems that the disease progression itself is the determinant of any future cartilage damage rather than intra-articular corticosteroid.

Studies in knee inflammatory arthritis have confirmed the benefit of strict non-weightbearing rest after injection. No studies in osteoarthritis have been performed but it is logical to advise a similar approach. Intra-articular corticosteroids should be used in disease flares only. Some studies suggest a greater benefit if a joint effusion is present in the knee. The effusion may indicate an active inflammatory phase of the disease with possible increased cartilage damage. American College of Rheumatology guidelines suggest no more than 3–4 knee joint injections per year. In patients needing more than this number, other therapeutic manoeuvres should be considered.

Hyaluronic acid derivatives
Hyaluronic acid is a high molecular weight polysaccharide, and is a major component of synovial fluid and cartilage. The molecular weight and amount of hyaluronic acid decrease in osteoarthritis. It was postulated that supplementation with intra-articular hyaluronic acid could help to improve synovial fluid viscoelasticity. Several preparations are available, either low (for example, Hylan) or high molecular weight (for example, Synvisc).

Studies have found Hylan (an injection each week for five weeks) and Synvisc (an injection each week for three weeks) to be superior to placebo in reducing pain and number of intra-articular corticosteroid injections needed for 12 months. Symptomatic effect started at week 3–5 and persisted up to 12 months. In comparison with intra-articular steroid, a double blind study found that hyaluronic acid and intra-articular corticosteroid had similar efficacy up to week 5, followed by superior efficacy of hyaluronic acid until the end of the six month study. There is also evidence that hyaluronic acid injections have similar efficacy to NSAIDs for between 3–6 months after injection. Data on the effect of repeated injections, cost benefit, and possible disease modifying effects are lacking. At the moment, most repeat injections are given on recurrence after a successful response to an initial course.

Box 3: NICE recommendations for the use of COX-2 selective inhibitors

- Aged over 65 years.
- Using other medicines known to increase the likelihood of gastrointestinal problems.
- Having serious co-morbidities.
- Requiring long term use of standard NSAIDs at the maximum dose.

These drugs should be prescribed after discussion with the patient and assessment of the risks and benefits for each patient.
Topical treatments

Topical capsaicin cream is often used on hands and knees in patients with moderate pain. There have been some trials showing the efficacy of capsaicin in osteoarthritis. There is little evidence of efficacy of topical NSAIDs.

**Glucosamine sulphate**

Glucosamine sulphate is a nutrient supplement available over the counter from pharmacies and health food shops in Europe and USA, and is used to relieve musculoskeletal symptoms. Many preparations are available, some of which also contain chondroitin sulphate.

Both glucosamine sulphate and chondroitin sulphate are derivatives of glycosaminoglycans found in articular cartilage. Their mechanism of action is unclear, especially as they cannot be absorbed from the gut intact. Reginster et al studied 212 patients with primary knee osteoarthritis and found that there was a 20%–25% improvement in symptoms and a reduction in knee medial compartment changes over three years in those taking glucosamine. A meta-analysis has also shown that glucosamine sulphate has some analgesic efficacy. Interestingly, a recent double blind placebo controlled trial found no clinical or statistical analgesic effect, and a large placebo response (33%). This trial included patients with a wider spectrum of disease severity and higher pain and disability scores than the Reginster trial. Glucosamine sulphate has probably an analgesic effect in mild to moderate knee osteoarthritis. There is little evidence for its use in osteoarthritis at other sites.

**Other possible disease modifying osteoarthritis drugs**

Diclofenac is a drug that inhibits production and activity of metalloproteinases and interleukins and may have an effect in delaying progression of hip osteoarthritis as measured by minimum joint space measured visually. There is also interest in the use of bisphosphonates and specific leukotriene antagonists as disease modifiers.

**Surgery**

Surgery is used where medical therapy has reached its limits. Arthroscopic debridement and lavage can improve symptoms in degenerative meniscal tears, but does not halt progression. Autologous cartilage transplantation, where grafts of normal cartilage are taken from the edge of the diseased joint, cultured in vitro and reimplanted into areas where the cartilage is denuded may be an effective technique, but it is expensive and is not currently recommended for first line treatment of knee joint articular cartilage defects. Osteotomy in early osteoarthritis may relieve symptoms and slow the rate of progression. Arthrodesis is good as a last resort for pain relief. It can be used in the carpus, spine, and foot. Joint replacement is, of course, the final solution for many people, providing pain free and functioning joints for up to 20 years.

**THE FUTURE**

Translational research from the bench to the bedside will hopefully allow the development of true disease modifying osteoarthritis drugs.

- Local delivery of anti-inflammatory cytokines (for example, IL-1 Ra) or gene induction using gene transfer methods may provide a novel treatment regimen.
- Further work on cartilage culture and transplantation for other joints is needed.

Large clinical trials to assess the efficacy of interventions are also necessary, using validated and reliable outcome measures that reflect disease activity, damage, and quality of life.

**CONCLUSION**

This review has detailed current knowledge about the epidemiology and best practice in treating osteoarthritis. At the moment most of our knowledge of the aetiology and epidemiology of osteoarthritis is from observational studies. Very little is really known with certainty about the mechanism(s) underlying osteoarthritis, why its course varies from person to person, and why it progresses rapidly in some and not in others. Our diagnostic measures are based on clinical findings and clumsy radiological methods and none of our therapeutic interventions are curative, with many patients needing joint replacements. Robust outcome measures are needed in order to assess the efficacy of any disease modifying osteoarthritis drug in the future. Currently such outcome measures are not agreed. This hampers research opportunities. Meanwhile, osteoarthritis remains a significant public health problem.


56 Hughes R, Carr A. A randomised, double-blind, placebo-controlled trial of glucosamine sulphate as an analgesic in osteoarthritis of the knee. Rheumatol 2002;41:279–84.

