Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper

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Background Paper 6.12
Osteoarthritis

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Executive Summary

Osteoarthritis (OA), the most common musculoskeletal condition, is a long-term chronic disease involving the thinning of cartilage in joints which results in bones rubbing together, creating stiffness, pain, and impaired movement. OA is related with age, but is associated with a variety of both modifiable and non-modifiable risk factors, including obesity, lack of exercise, genetic predisposition, bone density, occupational injury, trauma, and gender.

Osteoarthritis is a major cause of disability in elderly populations around the globe, especially in developed countries. The prevalence of OA is increasing and will continue to do so as the population increases, ages, and is subject to risk factors such as the obesity epidemic. As OA causes pain and impairs functionality of the patient, it places a major burden on individuals, communities, health systems, and social care systems.

The current control strategy mainly consists of palliative pain treatment, as there are several medicines on the market that alleviate pain and improve function in OA patients. In severe cases, joint replacement surgery has been proven effective in relieving the painful and debilitating effects of the disease, though the high cost and use of advanced resources mean these procedures are not available in many countries around the world. There are currently no therapies available that can reverse or halt the progression of osteoarthritis; larger studies are needed to evaluate the clinical and cost effectiveness of the few therapies that have shown promise in animal trials.

Another principal aspect of osteoarthritis care that requires further research is diagnostic techniques. The current methods of clinical diagnosis and X-rays are not precise enough to effectively measure status and progression of the condition, which presents serious difficulties in evaluating both the impact of risk factors and the effectiveness of potential therapies. The lack of valid biomarkers limits pharmaceutical development and clinical monitoring.

The issues presented by the lack of both reliable diagnostics and medicines that can reverse the progression of osteoarthritis must be addressed through further research in order to effectively reduce the large health and economic burden of osteoarthritis.

Key Updates Since 2004

- As the global population continues to age, the burden of osteoarthritis will increase dramatically.
- Some progress has been made in biomarkers for osteoarthritis diagnosis, but much more research still needs to be done before they can be used in a clinical setting.
- Meta-analyses of clinical trials show that avocado-soybean unsaponifiables significantly reduce pain associated with osteoarthritis and may be an effective complementary treatment that could be used in conjunction with traditional pharmaceuticals.
- While they are expensive operations, total hip and knee replacement surgeries have been shown to be cost effective in the long term. More research should be conducted on how to introduce low cost joint replacement surgeries into hospitals in low and middle income countries.

1. Introduction

In 2004, a report *Priority Medicines for Europe and the World* was written by Warren Kaplan and Richard Laing and published by the World Health Organization (WHO). A chapter (6.12) and background paper on osteoarthritis were written for this publication by Saloni Tanna.

Osteoarthritis is characterized by the breakdown of cartilage in joints.[1] As cartilage deteriorates, the bones of the joint begin to run against one another, causing stiffness and pain, which often impairs movement. Osteoarthritis also can damage ligaments, menisci, and muscles. Bone or cartilage fragments may float in the joint space, causing irritation and pain. Bone spurs, or osteophytes, may also develop, causing additional pain and potentially damaging surrounding tissues.[1] Around the world, an estimated 10%-15% of adults over 60 have some degree of osteoarthritis.[1] It most commonly affects the joints in the knee, hands, feet, and spine, and is also relatively common in other joints such as the shoulder and hip joints.[1]

There are two types of osteoarthritis: primary and secondary.

Primary osteoarthritis is a chronic degenerative disease that is related to, but not caused by, aging. As a person ages, the water content of their cartilage decreases, thus weakening it and making it less resilient and more susceptible to degradation. There are strong indications that genetic inheritance is a factor, as up to 60% of all OA cases are thought to result from genetic factors.[2]

Secondary arthritis tends to show up earlier in life, often due to a specific cause such as an injury, a job that requires kneeling or squatting for extended amounts of time, diabetes, or obesity. But though the aetiology is different than that of primary OA, the resulting symptoms and pathology are the same.[2]

The main symptoms are pain, loss of ability, and "joint stiffness after exercise or use." These symptoms are often aggravated by activity or rigorous exercise and relieved during rest, though the disease may eventually progress to the point where the patient even feels pain when resting, and some people report pain so intense that it wakes them up when they are sleeping.[2]

Osteoarthritis, at present, cannot be cured, and will likely get worse over time, but the symptoms can be controlled. Treatments vary widely, from alternative medicine, to lifestyle changes such as exercise and diet, to physical aids such as canes or braces, to medications such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDS), corticosteroids, and more. This range of treatments is elaborated on in section 6.12.3 of this OA chapter.[2]

2. Size and Nature of the Disease Burden

Osteoarthritis primarily affects the elderly population and is present worldwide. Because of its function-impairing nature, its burden on society is quite substantial both in terms of its epidemiology and its economic impact.

2.1 Epidemiology

Osteoarthritis is the single most common cause of disability in older adults.[3] It ranks as the fifth highest cause of years lost to disability in the whole population in high-income countries, and the ninth highest cause in low- and middle-income countries (See Figure 6.12.1). It accounts for 50% of the entire musculoskeletal disease burden, and thus is considered the highest-burden condition within the musculoskeletal group of diseases, which also includes rheumatoid arthritis and osteoporosis. Radiographic evidence of knee osteoarthritis is present in approximately 30% of men and women over the age of 65.[2] Worldwide estimates are that 9.6% of men and 18.0% of women over the age of 60 years have symptomatic osteoarthritis. Approximately 80% of those with OA will have limitations in movement, and 25% cannot perform their major activities of daily life.[4]

Figure 6.12.1: Leading global causes of years lost to disability by income group (2004)

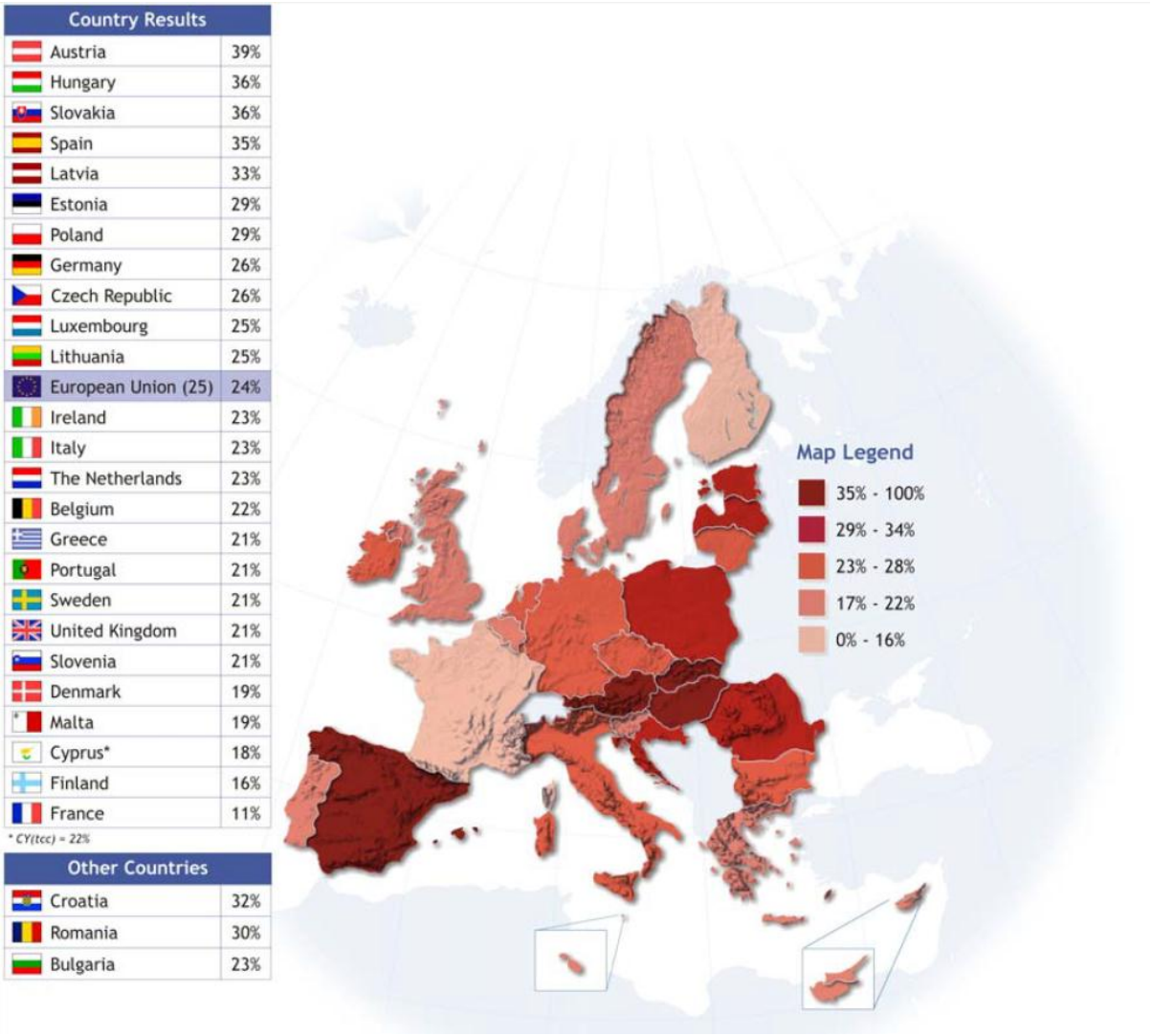
	Low- and middle-income countries				High-income countries		
	Cause	YLD (millions)	Per cent of total YLD		Cause	YLD (millions)	Per cent of total YLD
1	Unipolar depressive disorders	55.3	10.4	1	Unipolar depressive disorders	10.0	14.6
2	Refractive errors	25.0	4.7	2	Hearing loss, adult onset	4.2	6.2
3	Hearing loss, adult onset	23.2	4.4	3	Alcohol use disorders	3.9	5.7
4	Alcohol use disorders	18.4	3.5	4	Alzheimer and other dementias	3.7	5.4
5	Cataracts	17.4	3.3	5	Osteoarthritis	2.8	4.1
6	Schizophrenia	14.8	2.8	6	Refractive errors	2.7	4.0
7	Birth asphyxia and birth trauma	12.9	2.4	7	COPD	2.4	3.5
8	Bipolar disorder	12.9	2.4	8	Diabetes mellitus	2.3	3.4
9	Osteoarthritis	12.8	2.4	9	Asthma	1.8	2.6
10	Iron-deficiency anaemia	12.6	2.4	10	Drug use disorders	1.7	2.4

Source: World Health Organization. Global Burden of Disease Report: 2004. Part 3: Disease incidence, prevalence and disability.

The 2010 Global Burden of Disease Study published in the Lancet in December of 2012 reports that the burden of musculoskeletal disorders is actually much larger than in previous assessments of the global burden of disease. Previous reports estimated this group of disorders to account for approximately 2.0% of DALYs, while this report estimates it to be closer to 6.8%.[5] These data show that osteoarthritis and other musculoskeletal disorders are extremely common in all populations.[6]

Altogether 10%-15% of adults over 60 have some degree of osteoarthritis.[10] Across the EU Member States, diagnosed OA prevalence varies from 2.8% in Romania to 18.3% in Hungary.[7] Figure 6.12.2 illustrates the health resource use burden of osteoarthritis across Europe.

Figure 6.12.2: Percentages of people undergoing long-term medical treatment for muscle, bone, or joint problems.



Source: European Union. *Special Eurobarometer: Health in the European Union*, 2007.

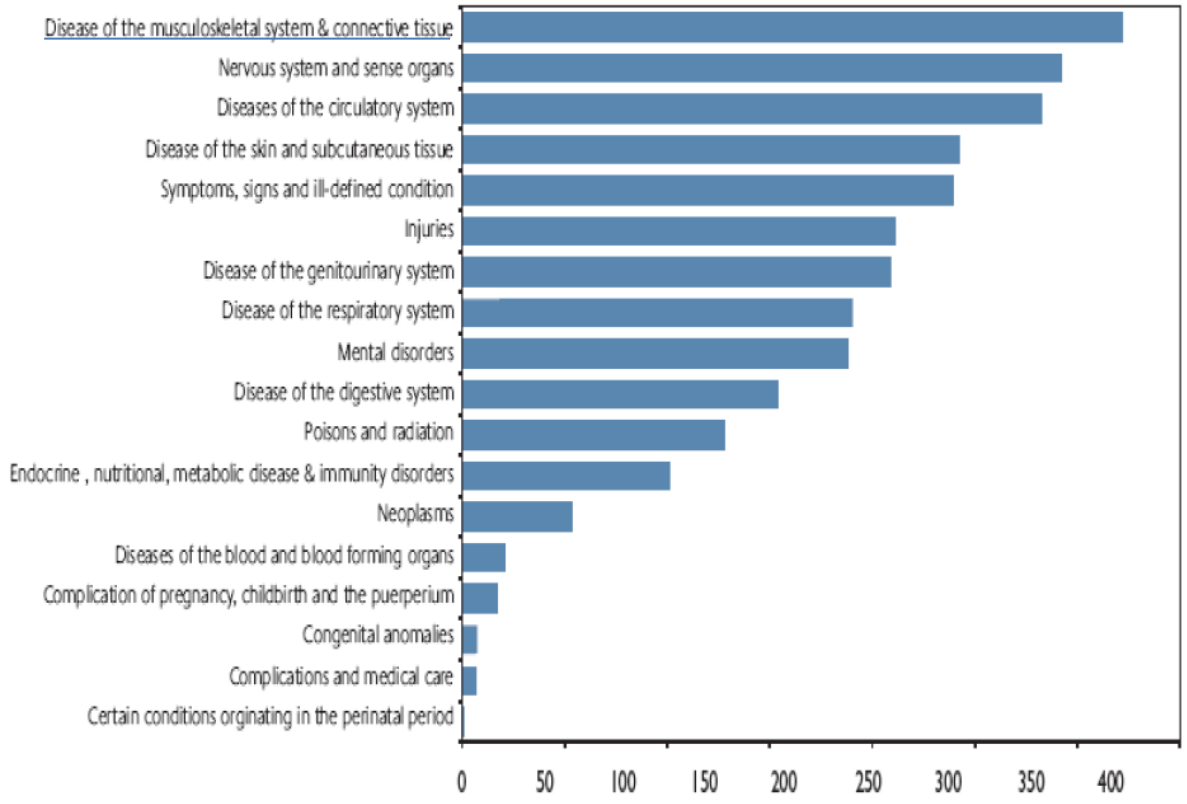
As the elderly population increases around the world, there is a consequent rise in the prevalence of non-communicable and chronic diseases (see Chapter 5). One of the major disabling conditions among the elderly population is musculoskeletal (MSK) diseases, such as osteoarthritis.[8] According to the United Nations, the proportion of people over the age of 60 will triple over the next 40 years, meaning this demographic will account for more than 20% of the world's population by 2050.[9] Of that 20%, a conservative estimate of 15% will have symptomatic osteoarthritis, and one third of these people will be severely disabled. This translates to 130 million people who will suffer from osteoarthritis and 40 million people who will be severely disabled by OA by 2050.[10]

Osteoarthritis is the most common form of arthritis in both developed and developing countries. However, the majority of patients in developing countries do not have access to joint replacement surgery, and as a result will have to endure severe disability for a substantial part of their lives, placing an enormous burden on their communities.[13]

2.2 Economic Burden

In terms of health resource use, 82.9% of patients with osteoarthritis had at least one investigative test over the previous six-month investigative period, and 7.9% of OA patients had purchased adaptive aids and devices over the same six-month period in a 2004 study.11[7] Total six-month costs related to OA were US$ 2456, with direct costs accounting for just over 80% of these costs. Almost half of all direct costs were attributable to drug costs, especially prescription drug costs. Of the patients surveyed, 30.7% were unable to do chores, and 3.6% of the patients had taken time off work in the past six months because of their condition.[11] See Annex 1 for further breakdown of healthcare resource use, and Annex 2 for elaboration of the cost of illness for patients with OA. Figure 6.12.3 below depicts the burden of musculoskeletal diseases on primary care in the United Kingdom.[11]

Figure 6.12.3: GP consultation rates for non-infectious diseases per 100,000 people



Source: European Musculoskeletal Conditions Surveillance and Information Network (EUMUSC). "Musculoskeletal Health in Europe: Report v5.0" 2012

2.3 Burden of Specific OA Treatments

Treatment of Pain

Data from a large claims database of a private insurer from 2003 to 2004 found that 15% of annual drug costs went to pain and pain-related medications. More than half (54%) of the patients in the study took a COX-2 inhibitor, 46% used non-selective NSAIDS, 34% were prescribed antidepressants, and 9% took tramadol.[12]

Viscosupplementation

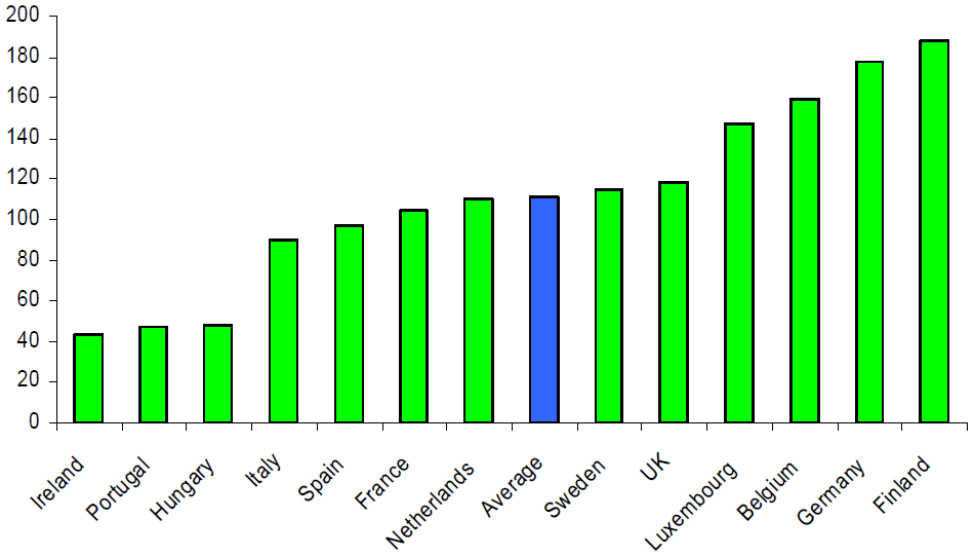
Little data is available regarding the effect of viscosupplementation, also known as intraarticular hyaluronate (IAH,) on total OA costs. A 2007 study in the U.S. estimated the actual cost of IAH to range from US$ 852 to US$ 1840 (including injections, arthrocentesis, and office visits) depending on the specific regimen.[13] IAH's purpose is often to delay joint replacement surgery.

Joint Replacement Surgery

The average age of a patient who receives a total hip replacement (THR) in the United States is just under 68 years of age, and the likelihood of having the surgery increases with age.[12] The same trend is apparent for total knee replacements (TKR). The number of hip and knee replacement surgeries performed is projected to continue increasing at a rapid rate: between 2005 and 2030, hip arthroplasties are expected to increase by 174%, and the number of knee arthroplasties is expected to increase even more rapidly: increasing by 673% by 2030.[12] Though joint replacement surgeries are expensive procedures, their high effectiveness may justify their prevalence, especially in high-income countries that have adequate resources for such treatments. The inpatient costs for primary THR are estimated to be around US$ 30 000; secondary or revision hip replacement costs are estimated to be around US$ 38,000. Similarly, primary TKR costs are estimated to be around US$ 21 000 and TKR revisions to cost approximately US$ 25 000.[12] Figures 6.12.4 and 6.12.5 depict the number of knee and hip replacement surgeries per 100 000 people in various European countries.

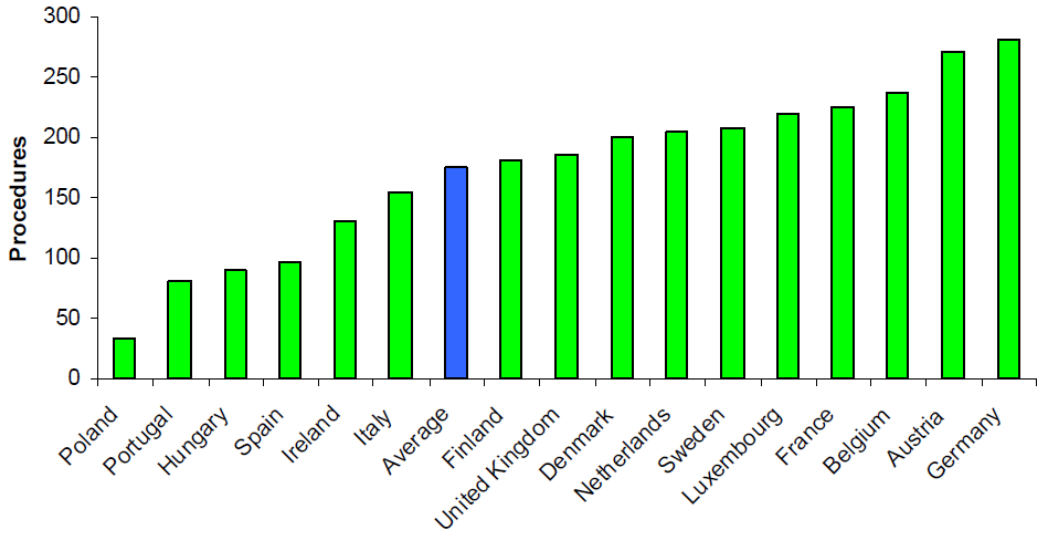
In summary, OA has widespread prevalence and sizeable economic costs (both direct and indirect) which causes it to have a substantial burden both in terms of health and economics around the globe.

Figure 6.12.4: Knee replacement procedures per 100,000 people in Europe (2006)



Source: European Musculoskeletal Conditions Surveillance and Information Network. "Musculoskeletal Health in Europe: Report v5.0" 2012

Figure 6.12.5: Hip replacement procedures per 100,000 people in Europe (2007)



Source: European Musculoskeletal Conditions Surveillance and Information Network. "Musculoskeletal Health in Europe: Report v5.0" 2012

3. Control Strategy

Patients with OA suffer from pain and loss of function. Objectives of OA management are to reduce the level of pain, reduce inflammation, slow cartilage degradation, improve function and reduce disability. This section reviews the overall control strategy for osteoarthritis, and is specifically divided into Prevention, Diagnosis, and Medical Management. Medical Management is further subdivided by nonpharmacological and pharmacological treatments.

3.1 Prevention

Because no highly effective pharmaceutical treatments exist and surgical options are expensive and not widely available, prevention is a major strategy in addressing the disease burden of osteoarthritis.

Primary prevention

Only a limited number of primary interventions have been identified for osteoarthritis, including:

- Weight control: Obesity is considered a risk factor for OA. Thus, maintaining or reducing weight through altered diet and increased physical exercise can lower the risk of developing OA. [14]
- Occupational injury prevention: Avoidance of repetitive joint use and proper management of related injuries can help prevent arthritis.[14]
- Sports injury prevention: Taking the necessary precautions to prevent injury such as warming up and using proper equipment can help reduce joint injuries.[14]
- Misalignment: Improper alignment of the knee or hip can contribute to osteoarthritis and proper treatment such as orthotics or bracing can help reduce the risk of developing the disease.[15]

Secondary prevention

The aim of secondary prevention is early diagnosis which allows for effective and appropriate interventions that will minimize the health consequences of the disease. Recently, research into bone and cartilage degradation has identified biochemical markers that may be used to identify OA early in the progression of the disease.[16] However, not enough is known about these biochemical markers to implement them in clinical practice. Currently, identification of arthritis is primarily done with X-rays or other imaging methods. But access to well-equipped health care facilities with X-ray technology is limited in many parts of the world.[17]

Tertiary prevention

Tertiary prevention focuses on minimizing the compilations of disease once it has been diagnosed. Such strategies for osteoarthritis are aimed at reducing pain and disability, and improving quality of life. Tertiary prevention strategies for OA include self-management (weight control, physical activity, and education), home help programs, cognitive behavioural interventions, rehabilitation services, and medical or surgical treatments.[14] See further elaboration in the section on Medical Management.

3.2 Diagnosis

As of 2004, biochemical markers of the disease were not available. However, more recent research has indicated that it may be possible to assess bone and cartilage using biochemical markers. Two processes that contribute to the development of osteoarthritis are bone degradation and cartilage degradation, and research has indicated that both of these two processes have potential biomarkers.

Bone Degradation

An osteoclast is a type of bone cell that degrades bone tissue by removing minerals and breaking up the organic bone; this process is called *bone resorption.* The majority of bone resorption by osteoclasts is mediated by the protease cathespin K, which specifically results in the fragmentation of collagen type I (CTX-I). The presence of CTX-I fragments has been used as a surrogate measure of bone resorption for *in vitro*, preclinical and clinical studies.[18]

Cartilage Degradation

An investigation of urinary concentrations of type-II collagen (CTX-II) fragments has revealed an association between these concentrations and the prevalence and progression of osteoarthritis of the knee and hip. Furthermore, these concentrations seem higher in patients with joint pain. Baseline CTX-II concentration was higher in subjects with baseline OA (see Table 6.12.1), and there were also associations between CTX-II and progression of OA (see Table 6.12.2).[18] It has been proposed that an assessment of collagen degradation be used as a quantitative measure of cartilage damage in assessing OA.[19]

Currently, the most common strategy to diagnose OA is a physical examination, which can show many of the symptoms of OA including crepitation (grating sound during joint movement), joint swelling, limited range of motion, tenderness where the joint is pressed, and pain during normal movements. Additionally, an X-ray of affected joints will show a loss of the joint space. In more advanced cases, there may be bone spurs or evidence of worn-down ends of the bones in the affected joint.[14] An MRI scan may be helpful in distinguishing OA from other kinds of injuries.[17] Artroscopy is a common method of diagnosis and monitoring of progression. It also combines an opportunity for therapeutic joint surgery at the same time. However, all these diagnostic tools have low sensitivity and specificity.

Given properly trained doctors, physical examinations are an inexpensive way to diagnose osteoarthritis around the world, though access to treatment may not be adequate. However, X-rays and similar imaging technologies are not available in many parts of the world.

Table 6.12.1: Cross-sectional association between baseline CTX-II concentration and baseline radiographic OA of the knee and/or hip

	Radiographic knee OA (n = 237)		Radiographic hip OA (n = 123)	
	Crude OR (95% CI)	Adjusted OR (95% CI)†	Crude OR (95% CI)	Adjusted OR (95% CI)†
Quartile (range of CTX-II values)‡				
First (1.49–2.10)	1	1	1	1
Second (2.11–2.25)	1.7 (1.0–2.9)	1.7 (1.0–2.9)	1.3 (0.7–2.5)	1.5 (0.8–2.9)
Third (2.26–2.39)	3.2 (2.0–5.2)	2.8 (1.6–4.6)	1.7 (0.9–3.1)	2.1 (1.1–4.0)
Fourth (2.40–3.11)	5.2 (3.3–8.4)	4.2 (2.5–7.0)	3.6 (2.0–6.2)	4.2 (2.2–7.8)
P for trend	<0.0001	<0.0001	<0.0001	<0.0001
Change in risk per SD§	1.9 (1.6–2.2)	1.7 (1.4–2.0)	1.8 (1.5–2.1)	1.8 (1.4–2.2)

* Associations are presented as odds ratios (ORs) with 95% confidence intervals (95% CIs) for risk of radiographic OA according to CTX-II levels. Knee and hip radiographic OA is defined as a Kellgren/Lawrence score ≥2 in at least 1 joint. See Table 1 for other definitions.
† For age, sex, body mass index, and lower limb disability index.
‡ Log transformed.
§ SD of mean log-transformed value.

Source: Reijman M, et al. A New Marker for Osteoarthritis: Cross-Sectional and Longitudinal Approach. *Arthritis and Rheumatism* Vol 50, No. 8, August 2004, pp2471-2478.

Table 6.12.2: Associations between baseline CTX-II concentration and radiographic progression of knee OA

	JSN ≥1.0 mm (n = 233)		JSN ≥1.5 mm (n = 73)		JSN ≥2.0 mm (n = 26)	
	Crude OR (95% CI)	Adjusted OR (95% CI)†	Crude OR (95% CI)	Adjusted OR (95% CI)†	Crude OR (95% CI)	Adjusted OR (95% CI)†
Quartile (range of CTX-II values)‡						
First (1.49–2.10)	1	1	1	1	1	1
Second (2.11–2.25)	1.0 (0.7–1.5)	0.9 (0.6–1.5)	1.5 (0.7–3.3)	1.3 (0.6–2.9)	3.7 (0.8–17.7)	4.1 (0.8–20.5)
Third (2.26–2.39)	1.2 (0.8–1.8)	1.1 (0.7–1.7)	1.9 (0.9–4.1)	1.5 (0.6–3.3)	3.6 (0.7–17.5)	4.5 (0.9–23.0)
Fourth (2.40–3.11)	1.2 (0.8–1.8)	1.1 (0.7–1.7)	2.5 (1.2–5.2)	1.8 (0.8–4.1)	5.2 (1.1–23.8)	6.0 (1.2–30.8)
P for trend	0.219	0.730	0.009	0.120	0.033	0.064
Change in risk per SD§	1.1 (1.0–1.3)	1.1 (0.9–1.3)	1.5 (1.1–1.8)	1.4 (1.0–1.8)	1.5 (1.0–2.2)	1.6 (1.0–2.5)

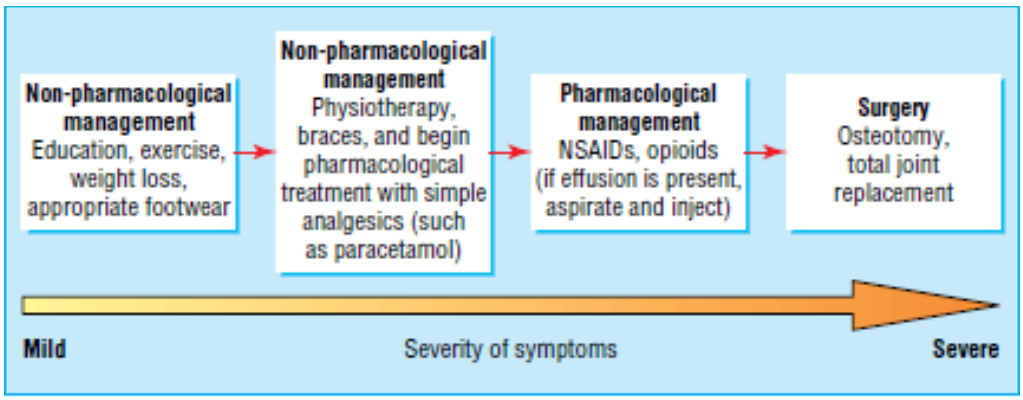
* Associations are presented as ORs and 95% CIs for risk of radiographic OA according to CTX-II levels. Joint space narrowing (JSN) is defined as the joint space width at baseline minus the joint space width at followup (medial and lateral compartments), using different cutoff points. See Tables 1 and 2 for other definitions.
† For age, sex, body mass index, lower limb disability index, baseline radiographic OA of the knee, and followup time.
‡ Log transformed.
§ SD of mean log-transformed value.

Source: Reijman M et al, A New Marker for Osteoarthritis: Cross-Sectional and Longitudinal Approach. *Arthritis and Rheumatism* Vol 50, No. 8, August 2004, pp2471-2478.

3.3 Medical Management

Persons affected by OA have a wide range of ages, demographics, disease impairment, comorbidities, and goals. Therefore management of the patient with OA should be comprehensive and individualized, taking into account the anatomical distribution, the phase and the progression rate of the disease. Comorbid conditions such as cardiac disease, hypertension, peptic ulcer disease or renal disease must be taken into account, as well as the patient's needs and expectations. The management plan of OA patients also needs to be regularly reviewed and adjusted in light of their response and adherence. This will vary between patients and location. The management of OA is broadly divided into non-pharmacological, pharmacological, and surgical treatments. The recommended hierarchy of treatment should be non-pharmacological treatments first, followed by pharmacological treatment and then surgery if the first two are unsuccessful (see Figure 6.12.6).[17] Examples of the different classes of therapies are outlined in Table 6.12.3.

Figure 6.12.6: recommended hierarchy of treatment options for OA.



Source: Hunter DJ, Felson D.T. Osteoarthritis: clinical review. *BMJ* 2006;332:639–42.

Table 6.12.3: Summary of therapeutic options in osteoarthritis

Non-pharmacological treatment
Education (patient and spouse or family) Social support Physical therapy Occupational therapy Weight loss Exercise Orthotic devises Pulsed EMF (Electromagnetic field therapy) Transcutaneous electrical nerve stimulation (TENS) Acupuncture Herbal remedies
Pharmacological treatment
Paracetamol/Acetaminophen NSAIDS (Non-steroidal anti-inflammatory drugs) [plus misoprostol or a proton pump inhibitor]* COX-2 inhibitors (cyclo-oxygenase-2 selective non-steroidal anti-inflammatory drugs)* Opioid analgesics Psychotropic drugs SYSADOA (Symptomatic Slow Acting Drugs for OA (avocado/soybean unsaponifiables (ASU), chondroitin, diacerein and glucosamine) Topical NSAIDS Topical capsaicin
Intra-articular treatment
Corticosteroids Hyaluronans Tidal irrigation
Surgical
Arthroscopy Osteomy UKR (unicompartmental knee replacement) Total joint arthroplasty (knee or hip)

Source: Hochberg MC et al, Guidelines for the medical management of osteoarthritis. Arthritis and Rheumatism. 2005; 38 (11): 1541-1546.
*Note: many COX-2 inhibitors were withdrawn due to side effects

3.3.1 Non-pharmacological Management

The first step of non-pharmacological management should be patient education. Patients should be counseled on coping skills, given resources for support, and encouraged to join self-management programs. Patients who are overweight or obese should be encouraged to

lose weight and increase their physical activity. Moreover, exercise is beneficial even to those patients who are at a healthy weight because increased muscle strength can reduce some of the complications of OA. Doctors should properly advise patients on low impact activities that will not increase their chance of exacerbating their OA symptoms. Non-pharmacological therapy also can include a referral to a physical therapist. Knee braces, orthotics, and appropriate footwear can reduce pain and improve function in people with poor alignment.[17]

Apart from the traditional non-pharmacological approaches, there has been recent research into other therapeutic options to treat OA. Of the newer therapies, pulsed ultrasound appears to be one of the most promising. A 2012 meta-analysis of 341 patients found that treatment had a significant effect on pain when compared to a placebo (mean difference on a visual analog scale from 0-10, -1.2 [95% CI -1.9 to -0.6]). No patients in any of the trials withdrew due to adverse effects, indicating that ultrasound is a very safe therapy.[20] In a 2010 Cochrane Review, acupuncture showed small but significant short term effects on pain (standardized mean difference of multiple scales -0.28, [95% CI -0.45 to -0.11]). However, many of these trials suffered from incomplete blinding.[21] A Cochrane Review completed in 2009 found potentially promising results of treatment with electromagnetic fields. Several of the individual trials conducted showed significant results but their clinical importance was questionable.[22] Transcutaneous electrical nerve stimulation, electro-acupuncture, and low level laser therapy all demonstrated clinically relevant pain relief in a 2007 systematic review (visual analog scale 0-100, 18.8 mm [95% CI 9.6 to 28.1], 21.9 mm [95% CI 17.3 to 26.5] and 17.7 mm [95% CI: 8.1 to 27.3]).[23]

3.3.2 Pharmacological Management

At present, there is no cure for OA. The primary strategy for pharmacological management of OA is to control pain and improve function and quality of life for the patient, while limiting drug toxicity. When OA pharmaceuticals are prescribed, the trade-offs between the risks and the benefits must be assessed because side effects are common and the long-term efficacy of these drugs is often variable or is yet to be determined.[17]

There are many pharmacological products on the market for the management of symptoms associated with OA. A review of the most common treatments is listed below.

Paracetamol (Acetaminophen)

Paracetamol (acetaminophen) is a commonly prescribed oral analgesic to treat mild to moderate OA pain. It has a relatively low level of short and long term side effects and can be taken up to four times daily.[20] However, a 2006 Cochrane Review found that acetaminophen is less effective than NSAIDs at treating moderate to severe OA pain (Table 6.12.4). But because adverse effects in some patients limit the wider use of NSAIDs, acetaminophen should still be an option.[24]

Table 6.12.4: Cochrane Review of Paracetamol Outcomes as measured by Standard Mean Differences on a variety of scales.

	Studies	SMD	Lower CI	Higher CI	Significant?
Pain	5	-0.13	-0.22	-0.04	yes
Adverse GI events		RR = -1.47	-1.08	-2.0	yes

Source: Towheed T, Maxwell L, Judd M, Catton M, Hochberg MC, Wells GA. Acetaminophen for osteoarthritis. Cochrane Database of Systematic Reviews 2006, Issue 1.

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are a large class of drugs which have analgesic and anti-inflammatory. Common oral NSAIDs include ibuprofen, aspirin, and naproxen. A Cochrane Review found NSAIDs to be more effective than placebo at treating OA pain.[25] However, treatment with NSAIDs is associated with gastrointestinal effects and potential toxicity, especially in the elderly. It has been recommended that the use of a gastrointestinal protectant in conjunction with NSAID treatment can reduce the risk of adverse effects.[21] A new class of NSAIDS called COX'2 inhibitors was introduced in 1999 with the aim of relieving pain and reducing gastro-intestinal side effects. However one of the class, refecoxib was found to increase the risk of cardiovascular events and was withdrawn in 2004. Celecoxib and eterocoxib remain on the market though with substantially reduced usage.

Topical NSAIDs

Topical NSAIDs, in the form of cream, patches, gels, solutions, have been found to be effective compared to placebo at reducing pain associated with musculoskeletal conditions, including OA. According to a Cochrane analysis, the most promising and effective topical NSAID drug appears to be diclofenac (Table 6.12.5). When compared to a placebo, patients who took diclofenac had significant reduction in pain (50% reduction in pain, RR 2.0 [95% CI 1.5 to 2.6]). The benefit of topical NSAIDs is that they eliminate the gastrointestinal side effects of oral treatment. However, they have been associated with certain local adverse effects and the current research indicates that they may be less efficacious than oral NSAIDs.[26]

Table 6.12.5: Cochrane Review of Pain Reduction with topical diclofenac

	Studies	Patients	RR	Lower CI	Higher CI	Significant?
Successful Treatment	4	569	2.0	1.5	2.6	yes

Source: Derry S, Moore RA, Rabbie R. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD007400

Opioids

Opioids have the ability to be used as alternatives for pain relief in patients who cannot use either NSAIDs or acetaminophen.[24] A large review of 11 clinical trials suggests that the small to moderate pain relieving effects of opioid treatment were outweighed by their adverse effects. The meta-analysis of 10 trials involving 2268 participants found that 4 times as many patients on opioid treatment dropped out due to negative side effects compared to those taking a placebo (RR 4.05 [95% CI 3.06 to 5.38]) (Table 6.12.6). The most serious adverse effect from opioid treatment is respiratory depression and overdosage while more mild side effects often include constipation, nausea, and itching.[27] Abuse potential is high with opioids.

Table 6.12.6: Cochrane Review of treatment outcomes with opiods.

	Studies	Patients	SMD	Lower CI	Higher CI	Significant?
Pain	10	2268	-0.36	-0.47	-0.26	yes
Function	10	2268	-0.33	-0.45	-0.21	yes
Drop outs due to adverse events	10	2268	RR = 4.05	3.06	5.38	yes

Source: Nüesch E, Rutjes AWS, Husni E, Welch V, Jüni P. Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD003115.

Diacerein

Diacerein is another pharmaceutical that can be used to control pain resulting from OA. A review of seven clinical trials found a small but consistent reduction in pain (weighted mean difference, -5.16 [95% CI-9.75, -0.57]) (Table 6.12.7). The authors concluded that more research should be done into the side effects of diacerein treatment given that the analysis found that 42% of patients in the treatment group experienced diarrhea.[28]

Table 6.12.7: Cochrane Review of Diacerein Outcomes

	Studies	Patients	WMD (0-100)	Lower CI	Higher CI	Significant?
Pain	5	1228	-5.16	-9.75	-0.57	yes

Source: Fidelix TS, Soares B, Fernandes Moça Trevisani V. Diacerein for osteoarthritis. Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD005117

Glucosamine

Glucosamine is an amino sugar found naturally in the body and comprises an important step in the synthesis of cartilage. There was hope that glucosamine might help to reverse the effects of OA, a task that have proved to be unsuccessful. A 2009 Cochrane Review found inconclusive results from glucosamine treatment. Some studies found that treatment improved both pain and function but others found no significant difference from the effects of placebo.[29]

Herbal therapies

Of all herbal therapies tested, avocado-soybean unsaponifiables have shown the most promising results in pain reduction (mean difference on a visual analog scale from 0-100, -8.06 [95% CI -11.53 to -4.60] (Table 6.12.8).[30] The current recommendation is that patients be given avocado-soybean unsaponifiables for a trial period of several months to see if they will benefit from its effects. Individual differences seem to play a large role in the effectiveness of avocado-soybean unsaponifiables, with patients with OA of the knee benefitting more than patients with OA of the hip.[31]

Table 6.12.8: Patient outcomes in Avocado/Soybean Unsaponifiables vs. placebo

	Studies	Patients	MD	Lower CI	Higher CI	Significant?
Pain	2	325	-7.61	-11.79	-3.42	Yes
Function	1	162	-13.20	-20.00	-6.40	Yes

Source: Herbal therapies: Little CV, Parsons T, Logan S. Herbal therapy for treating osteoarthritis. Cochrane Database of Systematic Reviews 2000, Issue 4. Art. No.: CD002947.

Intra-articular corticosteroids

Treatment with corticosteroids injected directly into the joint (intraarticular) has been shown to be effective, especially in OA of the knee. A 2009 Cochrane Review found intra-articular corticosteroids to be more effective than an intrarticular placebo at reducing pain at one week post injection (weighted mean difference on a visual analog scale from 0-100, -21.91 [95% CI -29.93 to -13.89]) (Table 6.12.9). However, questions still remain about the long term efficacy of treatment and the patient subgroups which will benefit most. [32]

Table 6.12.9: Patient pain outcomes in corticosteroids vs. placebo

	Studies	Patients	WMD	Lower CI	Higher CI	Significant?
1 week	3	161	-21.91	-29.93	-13.89	Yes
6 weeks	1	84	7.10	18.39	4.19	No

Source: Bellamy N, Campbell J, Welch V, Gee TL, Bourne R, Wells GA. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD005328

Viscosupplementation

Hyaluronan is a polysaccharide that is found naturally throughout the body and is one of the main components of the extracellular matrix. Viscosupplementation involves a series of injections of either hyaluronan or hylan products. It is thought that viscosupplementation changes the fluid of the joint in a way that increases the joint's function and reduces pain. A Cochrane Review indicated that the treatment was effective in reducing pain compared to a placebo at 5-13 weeks following treatment (weighted mean difference on a visual analog scale from 0-100, -9.04 [95% CI -14.10 to -3.98]) (Table 6.12.10). Treatment also appears to have a significantly positive effect on joint function and patient global assessment. However,

many of these studies had small sample sizes and thus more research is needed to definitively determine the efficacy of viscosupplementation.[33] In 2011, Bannaru et al reported on a systematic review of 54 eligible trials involving 7545 patients. They reported that intra articular injection of hyaluron was effective at four weeks, reached maximal effectiveness at eight weeks and still had detectable effect at six months after injection.[34]

Table 6.12.10: Pain improvement outcomes in patients treated with hyalgan versus placebo

	Studies	Patients	WMD	Lower CI	Higher CI	Significant?
Pain in walking after 5-13 weeks	14	1095	-9.04	-14.10	-3.98	Yes
Pain at rest after 5- 13 weeks	5	155	-9.65	-14.18	-5.13	Yes

Source: Bellamy N, Campbell J, Welch V, Gee TL, Bourne R, Wells GA. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD005321

S-Adenosylmethionine

S-Adenosylmethionine (SAMe) is a product that is often sold as a nutritional supplement in many parts of the world. A 2009 Cochrane Review of its effectiveness was inconclusive due to small sample sizes and poor quality data. A total of four studies with 542 patients failed to show any significant differences in outcomes measured by changes in pain intensity or function. Table 6.12.11 below summarizes these results. Adverse effects were not significantly different between intervention and control groups.

Table 6.12.11: Cochrane Review of SAMe Outcomes

	Studies	Patients	WSMD	Lower CI	Higher CI	Significant?
Pain	2	533	-0.17	-0.35	0.01	No
Function	3	542	0.02	-0.68	0.71	No

Source: Rutjes AWS, Nüesch E, Reichenbach S, Jüni P. S-Adenosylmethionine for osteoarthritis of the knee or hip. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD007321

The authors' conclusion was that SAMe should not be recommended until further trials of adequate sample size and methodology were undertaken.[35]

Autologous Chondrocyte therapy

Autologous chondrocyte implantation (ACI), involves the surgical implantation of healthy cartilage cells into the damaged areas. A 2010 Cochrane Review reported on six heterogeneous trials involving 442 participants. The authors conclusion was that there was insufficient evidence to draw conclusions on the use of ACI for treating full thickness articular cartilage defects in the knee. Further good quality randomised controlled trials with long-term functional outcomes are required.[36]

3.3.3 Surgical Management

When non-pharmacological and pharmacological management strategies are not effective at controlling OA symptoms, surgical options should be considered.

Joint replacement

Joint replacement is a serious and permanent intervention for patients who have few other options. Patients who experience severe daily pain and show extensive narrowing of joint space are eligible for joint replacement surgery. While this is an expensive treatment option, cost effective analyses have indicated that the costs from long term medication use and lost productivity outweigh the price of surgery in patients with severe symptoms.[17] A 2012 systematic review found that the estimated incremental cost-effectiveness ratio (ICER) for knee replacement in a United States Medicare-aged population varied from US$13 000 per QALY (quality-adjusted life year) over a five-year time horizon from the payer perspective to US$ 22 000 per QALY from the societal perspective and over the lifetime horizon. Table 6.12.12 summarizes the incremental cost-effectiveness ratio of total knee arthroplasty stratified by level of risk of perioperative complications. The 2012 study found the incremental cost-effectiveness ratio in a similar population of total hip arthroplasty patients to be similar.[37]

Table 6.12.12: incremental cost-effectiveness ratios of total knee arthroplasty (TKA)

TKA Status[b]	Cost	QALYs, No.[c]	ICER Compared With Next Least Expensive Strategy[d]	ICER Compared With No TKA[d]
Overall Population				
No TKA	37 100	6.822	NA	NA
TKA	57 900	7.957	18 300	NA
Stratified by Risk[e] of Perioperative Comorbidities				
Low-risk population				
No TKA	25 800	8.716	NA	NA
TKA	44 000	10.589	9700	NA
Medium-risk population				
No TKA	19 800	6.574	NA	NA
TKA	39 900	7.649	18 700	NA
High-risk population				
No TKA	86 800	5.713	NA	NA
TKA	111 500	6.594	28 100	NA
Stratified by Risk[e] of Perioperative Comorbidities and Hospital Volume				
Low-risk population				
No TKA	25 800	8.716	NA	NA
High	43 300	10.623	9200	9200
Medium	43 900	10.597	Dominated[f]	9600
Low	45 500	10.537	Dominated[f]	10 800
Medium-risk population				
No TKA	19 800	6.574	NA	NA
High	38 900	7.672	17 400	17 400
Medium	40 100	7.670	Dominated[f]	18 500
Low	41 700	7.585	Dominated[f]	21 700
High-risk population				
No TKA	86 800	5.713	NA	NA
Medium	110 600	6.608	26 600	26 600
Low	111 900	6.556	Dominated[f]	29 800
High	113 600	6.630	135 700	29 200

Abbreviations: ICER, incremental cost-effectiveness ratio (ratio of additional costs to additional benefits); NA, not applicable; TKA, total knee arthroplasty; QALY, quality-adjusted life year.

[a] All costs are reported as 2006 US dollars. All costs and QALYs are discounted at 3% annually.

[b] Low, medium, and high in this column refer to volume of TKA procedures (1-25, 26-100, and >200, respectively) performed annually in the evaluated hospitals.

[c] The QALY is a health outcome measure that combines quality of life, as determined by some preference-based valuation process, and length of life. One year in perfect health equals 1 QALY. One year in a health state rated as 70% of perfect health equals 0.7 QALY.

[d] For analyses stratified by more than 1 strategy, we present ICERs that compare each strategy with the next less expensive strategy and with the no-TKA strategy.

[e] Risk is defined as risk for complications.

Source: Daigle ME, Weinstein AM, Katz JN, Losina E. The cost-effectiveness of total joint arthroplasty: a systematic review of published literature. Best practice & research clinical rheumatology. 2012; 26: 649-658.

Osteotomy

Osteotomy is the cutting and reshaping of bones with the purpose of altering the area of the joint which bears weight. A Cochrane Review found that osteotomies reduced pain and improved function, though there is no evidence whether an osteotomy is more effective than conservative treatment.[38] There is also evidence that osteotomies may eliminate or delay the need for joint replacement surgery.[32]

Arthroscopic debridement and lavage

Arthroscopic debridement and lavage are two processes that involve removing damaged cartilage, bone, and excess debris surrounding the joint. This is still a very controversial process and a Cochrane Review found that the treatment did not improve pain or function when compared to a sham surgery. However, for specific population of patients, the surgery may be beneficial and more research is needed to identify these subgroups.[3]

4. Major Problems and Challenges for Disease Control (Why Does the Disease Burden Persist?)

Because there is such a wide variety of risk factors (see Table 6.12.12) for this disease, it is unlikely that OA can be prevented entirely. Protective factors such as exercise, healthy diet, and occupational injuries can all be addressed, but many risk factors such as gender, age, and genetics are not modifiable. The physical disability arising from pain and loss of functional capacity reduces quality of life and increases the risk of further morbidity. Though there is a wide range of devices and palliative medicines available that relieve pain and improve quality of life for patients, there is no pharmaceutical product that halts or reverses the onset of osteoarthritis.

Thus, as the population ages, the disease burden of osteoarthritis will naturally increase accordingly unless (1) primary prevention efforts such as healthy diet and exercise are scaled up around the world (2) diagnostics and secondary prevention methods are developed that detect the onset of OA very early, perhaps through testing genetic or biochemical markers, and (3) therapies are developed that stop or even reverse the progression of OA when it is identified. Otherwise, people around the world will continue to develop the currently-incurable disease, osteoarthritis.

Table 6.12.13: Risk Factors for Incidence and Progression of Osteoarthritis

Risk factor	Notes
Age	▪ Normal ageing processes cause increased OA progression ▪ Incidence increases with age but levels off around age 80
Trauma	▪ Collateral ligament, meniscal tears and joint fractures lead to increased risk for OA
Occupation	▪ More common in those performing heavy physical work ▪ Significant relationship between OA and occupational kneeling or repetitive use of joint during work ▪ Certain occupations, such as farming, construction work, physical education teaching, are risk factors for the development of OA
Exercise	▪ High-impact sports present an increase for knee OA
Gender and ethnicity	▪ Men under the age of 50 have a higher prevalence and incidence ▪ Women over 50 have a higher prevalence and incidence of OA than men of the same age ▪ Generally more common in Europeans than in Asians
Genetics	▪ There is genetic susceptibility to the disease ▪ Children of parents with early onset OA are at a higher risk of developing OA themselves
Obesity	▪ Strongest modifiable risk factor ▪ Overweight or obese people have almost 3 times the risk of developing OA as people with a normal weight (OR 2.96 [95% CI 2.56 to 3.43]) ▪ Weight loss can substantially decrease the risk of developing OA
Bone density	▪ Decreased bone mineral density is a risk factor for OA

Source: Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthritis and cartilage*. 2010; 18:24-33.

5. Past and Current Research into Pharmaceutical Interventions for Osteoarthritis

Currently all the treatment advances in OA offer palliative care and help to reduce the symptoms of pain. Unfortunately, there have been no new drugs that can prevent, halt or reverse OA progression, although pharmaceutical companies are actively pursuing development of such therapies. The following information summarizes the highlights of osteoarthritis over the past decade:

A US-based public-private partnership between the National Institutes of Health (NIH) and private industry companies, called the Osteoarthritis Initiative (OAI), was started in the early 2000s with the intention to combine resources for the purpose of finding biological markers related to the progression of OA.[34] Nearly 5 000 people who are either at risk of developing knee OA, in the early stage of the disease, or with more advanced OA are participating in the initiative at four centers around the United States. Participants provide biological specimens (blood, urine, DNA), images (X-rays and magnetic resonance scans), and clinical data such as dietary intake, medication use, pain, function, and other general health assessments. These patients are evaluated at 12-month intervals for five years; almost all of the patient records were complete as of December 2012. The preliminary data that has already been gathered from patients and is available online includes patient symptoms, measure of pain, nutrition, prescription medicines, and alternative therapies used by the participants.[39] When fully complete, the OAI should provide an "*unparalleled state-of-the-art database showing both the natural progression of the disease and information on imaging and biochemical biomarkers and outcome measures*".[40]

Another research initiative under Europe's FP7 is "Evaluation of Osteoarthritis Progression in a Patient-Specific Manner using Magnetic Resonance Imaging and Computational Modeling" (OAPROGRESS) was started in February 2012. Its objectives are to:

> *"(1) combine MRI with computational modeling for the estimation of stresses and possible failure points within human knee joints*
> *(2) develop second generation adaptive models of articular cartilage for the prediction of altered tissue structure and composition during OA progression. For the model validation, cartilage structure, composition and biomechanical properties as well as cell responses in situ are characterized. At the end of the project these main aims will be merged*
> *(3) estimate the effect of loading on cartilage degeneration during the progression of OA in a patient-specific manner."*[41]

The results of this study, expected to be finished in 2017,[40] will help in making decisions regarding clinical treatments and interventions for the prevention or further progression of osteoarthritis.

6. Opportunities for Future Research into New Pharmaceutical Interventions

There are currently no existing pharmaceutical therapies on the market that can prevent, reverse, or halt the progression of osteoarthritis. Without such medicines, the disease burden of osteoarthritis will naturally increase as the population continues to age. New analgesics therapies that are not disease modifying are in development and may offer an alternative approach to therapy. These products in development include NGF blockers such as tanezumab or fulranumab. Ion channel blockers most notably subtype selective sodium channel blockers (Nav1.7 and Nav1.8) and calcium channel blockers (N type and T type) are also in clinical development for pain indications including osteoarthritis. A 2012 Cochrane Review highlighted one therapy that has shown promising results: platelet-rich therapies (PRT) for long bone healing in adults.[37] There have been encouraging results from a number of in-vitro animal studies, but clinical evidence is thus far unclear. In human patients with osteoarthritis of the knee, those who received platelet-rich therapy had a higher proportion of healed bones after one year, as measured by X-ray (RR 2.67, 95% CI: 1.03 - 6.91). However, the 21-person study found no difference in patient-reported functional outcomes after one year. Thus, "while a potential benefit of platelet-rich therapies to augment bone healing in adults cannot be ruled out, the currently available evidence from a single trial is insufficient to support the routine use of this intervention in clinical practice. Future trials should focus on reporting patient-reported functional outcomes from all trial participants for a minimum follow-up of one year."[42]

Another area of research that may be translatable to the healing of osteoarthritis is applications of free radicals and reactive oxygen species (ROS). Free radicals are molecules or molecular fragments with an unpaired electron. This charge imbalance then makes the molecule highly reactive with adjacent molecules such as DNA, protein, and lipids, and can cause alterations in their structure. Under normal circumstances, ROS are produced during aerobic cell metabolism, help facilitate intracellular signalling, and play a role in priming the immune system. However, a 2009 study demonstrates that abnormal amounts of ROS results in oxidative stress and contributes to cartilage degradation.[43] These findings support the concept of antioxidant therapy to treat knee OA, though much research is needed in this area before it could be tested in the future.

A principal reason that drug developments to heal or stop OA have been lacking is that, in order to develop these therapies, issues regarding biomarkers, imaging techniques, and other diagnostic issues must first be addressed. The current evaluation methods (mainly X-rays, clinical diagnosis, and blood tests) are insufficient to precisely determine the progression and outcome of new treatments. Fifty per cent of patients in the general population with radiographic knee osteoarthritis do not report having pain. Furthermore, 50% of subjects who complain of knee pain, and who are at or above the age when osteoarthritis starts to become common (about 55 years), have no definite radiographic evidence of osteoarthritis.[44] As cartilage is radiolucent and destruction of cartilage is not possible to visualize, changes in the X-ray appearances of joints appear relatively late in pathogenesis of the disease. Experts in the field have expressed that further research into new imaging technologies, diagnostics, and biomarkers will be especially useful for the management of osteoarthritis. These areas are important because they will bridge the gap between basic science and clinical trials, and allow health professionals to determine:

- Who is likely to get osteoarthritis?
- How severe is the disease, and how quickly is it progressing?
- How is the patient responding to drugs, and which drugs are the most effective?

Additionally, there is a gap in the research surrounding the cost-effectiveness, safety, and efficacy of long-term OA management and the pharmaceutical therapies that are currently on the market. This information is important for patients, health professionals, policymakers, and other actors in the OA arena to know in order for them to make adequately informed decisions about care options for this disease.

The European League Against Rheumatism (EULAR) is an organization which represents the patient, health professional and scientific societies of rheumatology of all the European nations.[45] They aim to promote the research, prevention, treatment, and rehabilitation of rheumatic diseases, which they define as including rheumatic diseases of the connective tissue, locomotor, and musculoskeletal systems.[44] Their activities include an annual Congress, promoting education and translational research in the field of rheumatology, and partnering with European policymakers to develop policies and framework agendas,[44] such as the Framework Programmes.

Framework Programme 7, the current phase of the EU-funded Framework Programmes for Research and Technological Development, has a budget of over €50 billion over seven years to encourage research in the European Research Area. Almost €12 million of this budget has been allocated to the research initiative "Translational Research in Europe Applied Technologies for Osteoarthritis (Treat-OA)."[46] Treat-OA is a large-scale collaborative project to address the need for better treatment and diagnostics for OA. Their goal is to identify diagnostic and prognostic genetic markers for disease risk and progression and potential therapeutic targets (treatoa.eu) through the following key objectives:

1) *"Identify genes and biochemical markers consistently associated with the risk and progression of OA*
2) *Define the roles of these genes to further our understanding of the molecular pathways involved in disease aetiology*
3) *Analyze the molecular pathways to identify targets for pharmacological intervention*
4) *Develop in vivo models by the use of transgenic animal laboratory OA model systems*
5) *Develop a panel of genetic and biochemical diagnostics for risk and progression of OA*
6) *Disseminate results to the scientific community and use results and technologies for training within the EU Treat-OA will health develop European clinical and scientific excellence in the diagnosis and treatment of OA"* [47]

The knowledge derived from this initiative will provide valuable insight into the future direction of OA pharmaceutical research, as it will reveal novel drug targets and protein therapeutics for OA. There have been 55 published articles from this study so far,[48] including:

- Valdes AM, Evangelou E, Kerkhof HJM, et al."The GDF5 rs143383 polymorphism is associated with osteoarthritis of the knee with genomewide statistical significance**."** *Ann Rheum Dis.* Epub ahead of print.
- Evangelou E, Valdes AM, Kerkhof HJ, et al. "Meta-analysis of genome-wide association studies confirms a susceptibility locus for knee osteoarthritis on chromosome 7q22." *Ann Rheum Dis.* In press.

- van Meurs JB, Uitterlinden AG, Stolk L, et al. "A functional polymorphism in the catechol-O-methyltransferase gene is associated with osteoarthritis-related pain." *Arthritis Rheum.* 2009 Feb;60(2):628-9
- Valdes AM, McWilliams D, Arden NK, et al. "Different risk factors are involved in clinically severe large joint osteoarthritis according to the presence of hand interphalangeal nodes." *Arthritis Rheum.* 2010 May 24
- Castaño Betancourt MC, Cailotto F, Kerkhof HJ, et al. "Genome-wide association and functional studies identify the DOT1L gene to be involved in cartilage thickness and hip osteoarthritis." *Proc Natl Acad Sci U S A.* 2012 May 22;109(21):8218-23. Epub 2012 May 7

An additional area of therapy that is gaining popularity with consumer groups suffering from OA is complementary or alternative medicine. A Cochrane Review of herbal therapy for threating osteoarthritis concluded that "*the evidence for avocado-soybean unsaponifiables in the treatment of osteoarthritis is convincing, but evidence for the other herbal interventions is insufficient to either recommend or discourage their use*."[27] A Cochrane Review of acupuncture therapy for OA determined that there is a statistically significant benefit of such therapy, though it is quite small and may be partially due to placebo effects from incomplete blinding.[49] Larger-scale research is needed to evaluate the efficacy and cost-effectiveness of these therapies in all types of patients.

7. Conclusion

Osteoarthritis is a chronic progressive disease that is one of the leading causes of disability among elderly populations throughout the world. It causes pain, disability and impaired movement, which places a large burden (both in terms of health and economics) on individuals, communities, and health systems. While there are several therapies available for symptomatic treatment that mitigate pain, there are no medicines that can reverse or halt the progression of the disease. This pharmaceutical gap must be addressed in order to reduce the burden of OA.

One major reason for this gap is because there is a lack of effective biomarkers and diagnostics for OA, which makes it difficult to diagnose, track progression of, and monitor improvements in the patient's condition. These issues are especially important to address because OA is a condition that requires long-term careful management, so detailed information regarding the effectiveness of medicines is essential.
Future research should be directed at addressing this gap in diagnostics and biomarkers which will improve disease monitoring and allow the development of medicines that can reverse the progression of this high-burden condition.

References

[1] Haq I, Murphy E, Dacre J. Osteoarthritis. *Postgrad Med J* 2003;79:377–383.

[2] Teitel AD, Zieve D. MedlinePlud Medical Encycolpedia. National Institutes of Health. "Osteoarthritis." Last updated: Sept 26, 2011. http://www.nlm.nih.gov/medlineplus/ency/article/000423.htm

[3] Laupattarakasem W, Laopaiboon M, Laupattarakasem P, Sumananont C. Arthroscopic debridement for knee osteoarthritis. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD005118. DOI: 10.1002/14651858.CD005118.pub2.

[4] World Health Organization. "Chronic Rheumatic Conditions." Chronic diseases and health promotion. 2012. http://www.who.int/chp/topics/rheumatic/en/

[5] Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012 Dec 15;380(9859):2095-128.

[6] Murray CJL, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010 : a systematic analysis for the Global Burden of Disease Study 2010. The Lancet, Volume 380, Issue 9859, pp 2197-2223, 15 Dec 2012. doi:10.1016/S0140-6736(12)61689-4

[7] European Musculoskeletal Conditions Surveillance and Information Network. "Musculoskeletal Health in Europe: Report v5.0" 2012

[8] Fejer R, Ruhe A. "What is the prevalence of musculoskeletal problems in the elderly population in developed countries? A systematic critical literature review." *Chiropractic & Manual Therapies* 2012, 20:31 doi:10.1186/2045-709X-20-31.

[9] United Nations. World Population to 2300. Available at: http://www.un.org/esa/population/publications/.../WorldPop2300final.pdf

[10] Lim K, Lau C. "Perception is everything: OA is exciting." International Journal of Rheumatic Diseases 2011; 14: 111–112

[11] Maetzel A, Li LC, Pencharz J, Tomlinson G, Bombardier C, the Community Hypertension and Arthritis Project Study Team. "The economic burden associated with osteoarthritis, rheumatoid arthritis, and hypertension: a comparative study." *Ann Rheum Dis* 2004;63:395-401. DOI: 10.1136/ard.2003.006031.

[12] Bitton R. "The Economic Burden of Osteoarthritis." *American Journal of Managed Care* No 8. Vol 15: S230-S235. Sept 2009.

[13] Arnold W, Fullerton DS, Holder S, May CS. "Viscosupplementation: Managed Care Issues for Osteoarthritis of the Knee." *Journal of Managed Care Pharmacy* Supplement May 2007. Vol 13, No 4.

[14] Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthritis and cartilage*. 2010; 18:24-33.

[15] Neogi T, Zhang Y. Osteoarthritis prevention. *Curr Opin Rheumatol*. 2011; 23(2): 185–191. doi:10.1097/BOR.0b013e32834307eb.

[16] Schaller S, Henriksen K, Hoegh-Andersen P, Sondergaard BC, Sumer EU, Tanko LB, *et al.*: In vitro, ex vivo, and in vivo methodological approaches for studying therapeutic targets of osteoporosis and degenerative joint diseases: how biomarkers can assist? *Assay Drug Dev Technol* 2005, 3:553-580.

[17] Hunter DJ, Felson D.T. Osteoarthritis: clinical review. *BMJ* 2006;332:639–42.

[18] Reijman M, Hazes JMW, Bierma-Zeinstra SMA, Koes BW, Christgau S, Christiansen C, Uitterlinden AG, Pols HAP. "A New Marker for Osteoarthritis: Cross-Sectional and Longitudinal Approach." *Arthritis and Rheumatism* Vol 50, No. 8, August 2004, pp2471-2478.

[19] Nielsen Rh, Stoop R, Leeming DJ, Stolina M, Qvist P, Christiansen C, *et al*.: Evaluation of cartilage damage by measuring collagen degradation products in joint extracts in a traumatic model of osteoarthritis. *Biomarkers* 2008 Feb;13(1):79-87.

[20] Rutjes AWS, Nüesch E, Sterchi R, Jüni P. Therapeutic ultrasound for osteoarthritis of the knee or hip. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD003132. DOI: 10.1002/14651858.CD003132.pub2.

[21] Manheimer E, Cheng K, Linde K, Lao L, Yoo J, Wieland S, van der Windt DAWM, Berman BM, Bouter LM. Acupuncture for peripheral joint osteoarthritis. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD001977. DOI: 10.1002/14651858.CD001977.pub2

[22] Hulme JM, Welch V, de Bie R, Judd M, Tugwell P. Electromagnetic fields for the treatment of osteoarthritis. Cochrane Database of Systematic Reviews 2002, Issue 1. Art. No.: CD003523. DOI: 10.1002/14651858.CD003523.

[23] Bjordal JM, Johnson MI, Lopes-Martins RAB, Bogen B, Chow R, Ljunggren AE. Short-term efficacy of physical interventions in osteoarthritic knee pain: a systematic review and meta-analysis of randomized placebo-controlled trials. BMC musculoskeletal disorders. 2007; 8:51 doi:10.1186/1471-2474-8-51.

[24] Towheed T, Maxwell L, Judd M, Catton M, Hochberg MC, Wells GA. Acetaminophen for osteoarthritis. Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD004257. DOI: 10.1002/14651858.CD004257.pub2.

[25] Scott D, Kowalczyk A. Osteoarthritis of the knee. BMJ Clinical Evidence 2007;09:1121

[26] Derry S, Moore RA, Rabbie R. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD007400. DOI: 10.1002/14651858.CD007400.pub2.

[27] Nüesch E, Rutjes AWS, Husni E, Welch V, Jüni P. Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD003115. DOI: 10.1002/14651858.CD003115.pub3.

[28] Fidelix TS, Soares B, Fernandes Moça Trevisani V. Diacerein for osteoarthritis. Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD005117. DOI: 10.1002/14651858.CD005117.pub2.

[29] Towheed T, Maxwell L, Anastassiades TP, Shea B, Houpt JB, Welch V, Hochberg MC, Wells GA. Glucosamine therapy for treating osteoarthritis. Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD002946. DOI: 10.1002/14651858.CD002946.pub2.

[30] Little CV, Parsons T, Logan S. Herbal therapy for treating osteoarthritis. Cochrane Database of Systematic Reviews 2000, Issue 4. Art. No.: CD002947. DOI: 10.1002/14651858.CD002947.

[31] Christensen R, Bartels EM, Astrup A, Bliddal H. Symptomatic efficacy of avocado-soybean unsaponifiables (ASU) in osteoarthritis (OA) patients: a meta-analysis of randomized controlled trials. [Review]. *Osteoarthritis and Cartilage*. 2008;16:399-408.

[32] Bellamy N, Campbell J, Welch V, Gee TL, Bourne R, Wells GA. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD005328. DOI: 10.1002/14651858.CD005328.pub2.

[33] Bellamy N, Campbell J, Welch V, Gee TL, Bourne R, Wells GA. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD005321. DOI: 10.1002/14651858.CD005321.pub2.

[34] Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis--meta-analysis. Osteoarthritis Cartilage. 2011 Jun;19(6):611-9. doi: 10.1016/j.joca.2010.09.014. Epub 2011 Apr 9. Review.

[35] Rutjes AWS, Nüesch E, Reichenbach S, Jüni P. S-Adenosylmethionine for osteoarthritis of the knee or hip. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD007321. DOI: 10.1002/14651858.CD007321.pub2.

[36] Haris S Vasiliadis, Jason Wasiak, Autologous chondrocyte implantation for full thickness articular cartilage defects of the knee, *The Cochrane Library*, 2011 DOI: 10.1002/14651858.CD003323.pub3

[37] Daigle ME, Weinstein AM, Katz JN, Losina E. The cost-effectiveness of total joint arthroplasty: a systematic review of published literature. Best practice & research clinical rheumatology. 2012; 26: 649-658.

[38] Brouwer RW, van Raaij TM, Bierma-Zeinstra SMA, Verhagen AP, Jakma TT, Verhaar JAN. Osteotomy for treating knee osteoarthritis. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD004019. DOI: 10.1002/14651858.CD004019.pub3.

[39] National Institutes of Health. "Osteoarthritis Initiative Releases First Data." Aug 2006. http://www.nih.gov/news/pr/aug2006/niams-01.htm Accessed 4 Dec. 2012.

[40] Osteoarthritis Initiative. "Study Overview and Objectives." 2011. http://oai.epi-ucsf.org/datarelease/StudyOverview.asp Accessed 4 Dec. 2012.

[41] Community Research and Development Information Service for Science, Research, and Development (CORDIS). "Evaluation of Osteoarthritis Progression in a Patient-Specific Manner using Magnetic Resonance Imaging and Computational Modeling." Record control number: 101150.

[42] Griffin XL, Wallace D, Parsons N, Costa ML. Platelet rich therapies for long bone healing in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 7. Art. No.: CD009496. DOI: 10.1002/14651858.CD009496.pub2.

[43] Sutipornpalangkul W, Morales NP, Harnroongroj T. "Free Radicals in Primary Knee Osteoarthritis." *J Med Assoc Thai* 2009; 92 (Suppl 6): S268-74.

[44] Peat G, McCarney R, Croft P. "Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care." *Ann Rheum Dis* 2001;**60**:91-97 doi:10.1136/ard.60.2.91.

[45] European League Against Rheunmatism. "Structure of EULAR organisation." Accessed 11 Dec 2012 http://www.eular.org/

[46] Community Research and Development Information Service for Science, Research, and Development (CORDIS). "Translational research in Europe applied technologies for osteoarthritis." Record control number 88151.

[47] Translational Research in Europe Applied Technologies for Osteoarthritis. "About TreatOA." http://www.treatoa.eu/aboutTOA.html. Accessed 4 Dec. 2012.

[48] Translational Research in Europe Applied Technologies for Osteoarthritis. "Articles." http://www.treatoa.eu/publications.html . Accessed 5 Dec. 2012.

[49] Manheimer E, Cheng K, Linde K, Lao L, Yoo J, Wieland S, van der Windt DAWM, Berman BM, Bouter LM. Acupuncture for peripheral joint osteoarthritis. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No.: CD001977. DOI: 10.1002/14651858.CD001977.pub2.

Annexes

Annex 6.12.1: Use of healthcare resources by patients with osteoarthritis

Table 2 Use of healthcare resources by patients with RA, OA, and hypertension in a 6 month period

	RA (n = 253)		OA and HBP (n = 191)		OA (n = 140)		HBP (n = 142)	
	No (%)	Mean (range)	No (%)	Mean (range)	No (%)	Mean (range)	No (%)	Mean (range)
At least one visit to a health professional	253 (100)		191 (100)		140 (100)		142 (100)	
Family physician visits	215	4.8 (1–33)	191	4.4 (1–22)	140	4.2 (1–24)	142	4.3 (1–15)
Non-surgical specialist visits	253	4.2 (1–35)	67	2.6 (1–13)	60	2.4 (1–23)	40	2.1 (1–9)
Surgical specialists	87	2.0 (1–10)	55	1.6 (1–7)	42	1.8 (1–12)	32	1.5 (1–4)
Allied health professionals	97	9.4 (1–60)	66	9.5 (1–40)	55	8.6 (1–36)	35	9.3 (1–48)
Dentists	115	1.8 (1–9)	34	1.6 (1–4)	33	1.6 (1–6)	40	1.3 (1–3)
At least one test or investigation	239 (94.5)		147 (77.0)		116 (82.9)		104 (73.2)	
x Ray	117	2.3 (1–12)	76	1.4 (1–5)	68	1.5 (1–4)	36	1.5 (1–13)
CT or MRI	7	1 (N/A)	8	1.1 (1–2)	8	1.3 (1–2)	6	1.2 (1–2)
Ultrasound	40	1.2 (1–2)	21	1.2 (1–3)	11	1.2 (1–2)	15	1.1 (1–2)
Electrodiagnostic tests (ECG, etc)	17	1.2 (1–3)	15	1.2 (1–3)	13	1.2 (1–2)	15	1.2 (1–3)
Laboratory tests	228	5.3 (1–27)	98	2.0 (1–26)	84	1.8 (1–12)	79	1.9 (1–7)
Bone density	23	1.0 (1–2)	15	1.0 (1–1)	10	1.1 (1–2)	6	1.0 (1–1)
Other tests or investigations	26	2.1 (1–25)	17	1.2 (1–4)	9	1 (1–1)	5	1.2 (1–3)
Patients hospitalised	9 (3.6)		9 (4.7)		7 (5.0)		5 (3.5)	
Took drugs	253 (100)	9.0 (2–28)	191 (100)	7.5 (1–18)	140 (100)	6.7 (1–17)	142 (100)	6.3 (1–16)
Arthritis drugs	253	3.6 (1–7)	182	1.7 (1–4)	131	1.8 (1–4)	116	1.4 (1–5)
Antihypertensive drugs	72	1.6 (1–4)	182	1.9 (1–5)	38	1.6 (1–3)	141	1.9 (1–5)
Gastroprotective drugs	97	1.1 (1–3)	61	1.1 (1–2)	45	1.1 (1–2)	23	1.2 (1–3)
Complementary medicine products	227	3.0 (1–12)	159	2.6 (1–7)	117	2.9 (1–10)	106	2.6 (1–12)
Other drugs	198	2.5 (1–13)	157	2.8 (1–10)	116	3.0 (1–9)	109	2.5 (1–7)
Community services used	27 (10.7)	6.0 (1–30)	23 (12.0)	4.9 (1–15)	16 (11.4)	6.0 (2–23)	2 (1.4)	7.0 (2–12)
Adaptive aids or devices purchased	50 (19.8)	1.9 (1–7)	13 (6.8)	1.1 (1–2)	11 (7.9)	1.1 (1–2)	1 (0.7)	1 (N/A)
Unable to do chores (h)	135 (53.4)	207.5 (2–1186)	58 (30.4)	124.1 (3–800)	43 (30.7)	243 (6–1440)	18 (12.7)	172 (20–540)
Needed paid help	68 (26.9)	N/A	30 (15.7)	N/A	11 (7.9)	N/A	10 (7.0)	N/A
Needed unpaid help (h)	149 (58.9)	202 (2–1638)	31 (16.2)	112.2 (4–444)	24 (17.1)	162.7 (12–626)	18 (12.7)	134.0 (23–728)
Patient time off work (h)	42 (16.6)	136.9 (6–1208)	1 (0.5)	160 (N/A)	5 (3.6)	77.2 (8–128)	6 (4.2)	272.1 (24–760)
Caregiver time off work (h)	16 (6.3)	46.8 (3–336)	1 (0.5)	2 (N/A)	1 (0.7)	18 (N/A)	0 (0.0)	8.0 (8.0–8.0)

RA, rheumatoid arthritis, OA, osteoarthritis, HBP, high blood pressure (hypertension).

Source: Maetzel A, Li LC, Pencharz J, Tomlinson G, Bombardier C, the Community Hypertension and Arthritis Project Study Team. "The economic burden associated with osteoarthritis, rheumatoid arthritis, and hypertension: a comparative study." *Ann Rheum Dis* 2004;63:395-401. DOI: 10.1136/ard.2003.006031.

Annex 6.12.2: Economic burden of osteoarthritis.

Table 3 Cost of illness estimates for 6 months

	RA (n = 253)		OA and HBP (n = 191)		OA (n = 140)		HBP (n = 142)	
	$	%	$	%	$	%	$	%
Total costs	4674		2456		2856		1963	
Direct costs: total	*2575*	*55.1*	*2024*	*82.4*	*1976*	*69.2*	*1536*	*78.3*
Drugs: total	1237		974		768		786	
Arthritis drugs	769	62.2	143	14.7	163	21.2	59	7.5
Antihypertensive drugs	52	4.2	304	31.2	60	7.8	283	36.0
Gastroprotective drugs	110	8.9	96	9.9	88	11.5	50	6.4
Complementary medicine products	66	5.3	47	4.9	51	6.7	32	4.1
Other prescription drugs	240	19.4	383	39.4	406	52.9	361	46.0
Health professionals: total	554		339		384		316	
Family doctors	71	12.8	113	33.3	110	28.6	115	36.4
Non-surgeon specialists	146	26.3	58	17.0	69	17.9	50	15.9
Surgeon specialists	55	9.9	31	9.1	27	6.9	24	7.6
Dentists/dental surgeons	227	40.9	82	24.1	109	28.3	83	26.3
Allied health professionals	56	10.1	56	16.5	70	18.2	44	13.8
Separately ordered tests: total	278		110		119		100	
Hospitalisations: total	264		393		439		313	
Inpatient hospitalisation costs	153	57.8	243	61.9	300	68.4	237	75.8
Outpatient visit costs	86	32.5	64	16.2	60	13.7	27	8.8
Additional OHIP billings	25	9.6	86	21.9	79	18.0	48	15.4
Community services	186	–	203	–	219	–	19	–
Aids and devices	57	–	6	–	47	–	3	–
Indirect costs: total	*2098*	*44.9*	*432*	*17.6*	*880*	*30.8*	*427*	*21.7*
Lost time doing chores incl. paid help	1729	82.4	418	96.8	845	96.0	262	61.4
Time lost from work	326	15.5	14	3.2	33	3.8	164	38.3
Support person time lost from work	44	2.1	0	0.0	2	0.2	1	0.3

OA, osteoarthritis, HBP, high blood pressure (hypertension).

Source: Maetzel A, Li LC, Pencharz J, Tomlinson G, Bombardier C, the Community Hypertension and Arthritis Project Study Team. "The economic burden associated with osteoarthritis, rheumatoid arthritis, and hypertension: a comparative study." Ann Rheum Dis 2004;63:395-401. DOI: 10.1136/ard.2003.006031.