Clinical Guidelines for Managing Lower-limb Osteoarthritis in Hong Kong Primary Care Setting

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Executive Summary

Osteoarthritis (OA) is the most common form of arthritis in the world. Joint symptoms and/or back pain were amongst the top 10 commonest reasons for general practice consultation and cases attending Accident and Emergency departments classified as primary care cases (Lee, 1995; Lee, 2001).

Although there is no known cure for OA, the goals of the contemporary management of the patient with OA continue to include control of pain and improvement in function and health-related quality of life, with avoidance, if possible, of toxic effects of therapy.

The Family Medicine Unit of Department of Community and Family Medicine, the Chinese University of Hong Kong, has established an ad hoc committee to review the recent developments in the field and update the recommendations, in order to improve patient outcomes in the primary care setting by maximizing treatment efficacy and minimizing rates of adverse events. The committee followed the principles of evidence-based medicine as used in the process of making clinical decisions (Guyatt, 1998).

This guideline addresses the appropriate use of non-pharmacological and/ or pharmacological treatment of patients with osteoarthritis in the primary care setting. The key messages of the guidelines are as follow:

- Doctors in primary care must take a more active role in communicating with patients about available treatment options, their benefits and risks;
- Non-pharmacologic interventions should form an integral part of the treatment of OA but the optimal treatment requires combination with pharmacologic

measures;

- Acetaminophen is recommended as the first-line treatment for mild-to-moderate pain of OA, because of its efficacy, safety and cost and it is the preferred essential component of long term pain control.
- If acetaminophen is inadequate, alternative treatment options include NSAIDs, CSIs, SYSADOAs, opioids and injection treatments.

The guidelines are divided into three parts for dissemination. The first part is a summary of recommendations for managing OA knee and hip in primary care setting. The second part is a full report details the methodology and findings on which the recommendations are based. The last part is a patient education booklet (in Chinese) that will facilitate the implementation of the guidelines.

I) Objectives of the guidelines

- To examine the current level of evidence attributable to the non-pharmacological and pharmacological therapeutic modalities used in the treatment of knee and hip OA
- To systematically develop recommendations to assist clinician and patient decisions about appropriate health care for osteoarthritis in Hong Kong, especially for primary care physicians.
- To improve the quality of health care for osteoarthritic patients

II) Methodology

Guideline development committee

Guideline development committee comprised of three broad classes of members - relevant medical professionals (family physicians), hospital specialists (consultants in rheumatology, orthopaedics, geriatrics and a pharmacist) and specialist resources (experts in guideline methodology).

Search strategy

Searches were undertaken using Medline, Embase and, where appropriate, Cochrane Library. Using a combination of subject heading and free text terms, the search strategies located guidelines, systematic reviews and meta-analyses, randomised controlled trials, controlled trials and observational studies. The searches were conducted for the period 1966 to May 2004. The search strategies were backed up by the expert knowledge and experience of group members.

Selection of manuscripts

All studies that assessed the effects of a treatment for knee and hip OA on pain and/or function were included. The quality of relevant studies retrieved and their ability to provide valid evidence had been assessed. Assessment of the quality of studies considered issues of internal, external, and construct validity (Cook, 1979). The criteria used are shown in the box. Once individual papers had been assessed for methodological rigor and clinical importance, the information will be summarized. 27 guidelines (Appendix I), 39 systematic reviews / meta-analysis (Appendix II) and 54 RCT / controlled trials (Appendix III) were included and evaluated.

Criteria for assessing quality of randomised trials

- Appropriateness of inclusion and exclusion criteria
- Concealment of allocation
- Blinding of patients
- Blinding of health professionals
- Objective or blind method of data collection
- Valid or blind method of data analysis
- Completeness and length of follow up
- Appropriateness of outcome measures
- Statistical power of results

Categorising evidence

Summarised evidence had been categorised according to study design, and reflects susceptibility to bias. The box shows the categories in descending order of importance. Categories of evidence were adapted from the classification of the United States Agency for Health Care Policy and Research (SOLVD Investigators, 1991).

Categories of evidence

Ia_Evidence from meta-analysis of randomised controlled trials

Ib_Evidence from at least one randomised controlled trial

IIa_Evidence from at least one controlled study without randomisation

IIb_Evidence from at least one other type of quasi-experimental study

III_Evidence from descriptive studies, such as comparative studies, correlation studies and case-control studies

IV_Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

Strength of recommendation

Informal consensus methods had been used to derive recommendations, and reflect the certainty with which the effectiveness of a medical intervention can be recommended. Recommendations have been based upon consideration of the following: the strength of evidence, the applicability of the evidence to the population of interest, economic considerations, values of the guideline developers and society, and guideline developers' awareness of practical issues. The relation between the strength of a recommendation and the category of evidence is shown in the box.

Strength of recommendation
A_Directly based on category I evidence
B_Directly based on category II evidence or extrapolated recommendation from category I evidence
C_Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D_Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

III) Results

Non-pharmacological management

1) Patient Education

Patient education, which may provide useful information on the disease process, nature, prognosis, investigation and efficacy of management, is an important intervention for patients with chronic disease. It is effective to reduce pain, disability and increase coping skills of the OA patients (Lorig, 1993). There have also been shown that participants have fewer arthritis-related visits to doctors, increased physical activity and improved quality of life (Superio-Cabuslay, 1996). The provision of patient education was found to be economical as well as cost saving in terms of fewer usage of primary care ((Mazzuca, 1999). The meta-analysis confirmed that patient education interventions can provide additional benefits that are 20-30% as great as the effects of NSAID treatment for pain relief in OA (Superio-Cabuslay, 1996). The effective education techniques include regular telephone calls, group education, spouse assisted coping skills and education programs designed for individual needs (Jordan, 2003).

2) Weight Loss

Strong evidence about the role of body weight in the development and progression of knee OA has been found. Furthermore, obesity is found to be a clear risk factor for developing OA. A population study illustrated that obese individuals had four to five times the risk of knee OA than those of comparable age who were not obese (Anderson, 1988). This finding was supported by radiological evidence that showed that overweight and knee OA were related (Schouten, 1992; Felson, 1997).

Considering a force of about three to six times the body weight is normally exerted to the knee in walking, it can be deduced that an increase in stress from overweight and obesity could hasten the breakage of articular cartilage in the knee (Felson, 1995; Creamer, 1997). A long term follow up study showed that modest weight loss reduced the risk of developing symptomatic knee OA with a weight loss of 5kg in women will reduce the risk of symptomatic knee OA by 50% (Felson, 1992). Other studies also showed that modest weight loss has significant short-term and long-term symptomatic improvement for OA patients (Toda, 1998; Messier, 2000) and there is additional benefit for the OA patients with modest loss plus moderate exercise (Messier, 2004). In elderly male subjects, a reduction of body weight from the obese and the overweight categories to the normal weight category would decrease knee OA by 21.5%. The result is evenly more pronounced in females when the decrease is 33% (Felson, 1997). Therefore, weight reduction should play a key role of managing OA and OA patients should be counselled to lose weight in order to reduce the severity of joint pain and disability (Davis, 1990).

3) <u>Exercise / Physiotherapy</u>

Muscle weakness, loss of motion and pain are the common symptoms around the involved joint of the OA patients, there are 3 main goals for provide exercise programs to them (Brandt, 1998):

1. Reduction of impairment and improvement of function (reduction of joint pain, increases in range of motion and strength, normalization of gait, and facilitation of the performance of daily activities);
2. Protection of the joint from damage by reducing stress on the joint, attenuating joint forces, and improving biomechanics;
3. Prevention of disability and poor health secondary to inactivity by increasing the

daily level of physical activity and improving physical fitness.

A systematic review of exercise programmes shows a small to moderate reduction of pain and disability, regardless of the type of exercise (van Baar, 1999).

A) Manual therapy

Manual therapy refers to the passive movements that are applied by the physiotherapist with the purpose of increasing joint motion or reducing joint stiffness. Techniques may include passive range of motion, passive accessory joint motions, muscle stretching or soft-tissue mobilization and message (Fitzgerald, 2004). A randomized controlled trial to evaluate the effectiveness of manual therapy for osteoarthritis of the knee concludes that a combination of manual physical therapy and supervised exercise is effective in improving walking distance and decreasing pain, dysfunction, and stiffness in patients with osteoarthritis of the knee (Deyle, 2000).

B) Aerobic exercise

Aerobic exercises (such as walking, biking, swimming, aerobic dance and aerobic pool exercises) can increase the OA patients' aerobic capacity, muscle strength and exercise endurance, less exertion at a given work load, weight loss and the drug consumption can also be reduced (Brandt, 1998). A systematic review showed that aerobic exercise is effective with regard to pain relief and improvement in function of the OA joints, whilst long-term exercise can stop the decline of physical function (van Baar, 1999).

C) Strengthening exercise

Strengthening exercise has similar effect as aerobic exercise in improvements in

disability, pain and performance (Ettinger, 1997). RCTs recorded significant improvements in pain and functional improvement, compared with controls (O'Reilly, 1999; Ettinger, 1997; Rogind, 1998; Schilke, 1996). There are different kinds of strengthening exercises (Baker, 2000):

a) Isometric contraction exercises – limited to a small range around the joint angle of training;

b) Isotonic and isokinetic exercises – the joint moves through a specified range against a non-varying and varying external resistance.

A recent randomized controlled trial compared the effect of these exercises and concluded that isometric, isotonic or isokinetic muscle-strengthening exercise can reduce the pain and disability and improve the walking speed of the OA patients. The isotonic exercise has greater improvement in the pain relief and it is suggested for initial strengthening in patients with OA with exercise knee pain. The isokinetic exercise has the greatest increase of walking speed and decrease of disability after treatment and at follow-up, so it is suggested for improving joint stability or walking endurance at a later time (Huang, 2003).

With all exercise programmes, adherence is an issue. Though it is common to refer the OA patients for supervised physiotherapy classes, RCTs had showed that such improvement can also be achieved with home-based exercise (O'Reilly, 1999; Thomas, 2002).

D) Acupuncture

Acupuncture has been widely applied as complementary therapy for the OA patients and a systematic review concluded that it is effective in reducing pain; however, it is

not superior to sham-needling (Ernst, 1999). It has been concluded that the electro-acupuncture (EA) could reduce the OA pain and stiffness and the effect could last for more than 1 month (Tukmachi, 2004). A randomized controlled trial comparing the efficacy of EA with diclofenac as a symptomatic treatment of OA knee, found that EA is significantly more effective than placebo and diclofenac in pain relief and functional index, but the combination of EA and diclofenac treatment is not more effective than EA treatment alone (Sangdee, 2002).

Pharmacological management

1) Acetaminophen / Paracetamol

Acetaminophen should be the first step in the pharmacologic management of pain for patients with OA (Bijlsma, 2002). It was more effective than the placebo (Amadio, 1983) and was found that 4g/day of acetaminophen, 1200mg/day of ibuprofen and 2400mg/day of ibuprofen had similar effect (Bradley, 1992), even in patients with severe knee pain (Bradley, 2001). It could be used up to 2600mg/day for 2 years without significant adverse outcomes and as effective as 750mg/day of naproxen (Williams, 1993).

Although some randomised controlled trials (RCTs) concluded that NSAIDs/Coxibs are more effective on relieving OA pain than acetaminophen (Pincus, 2001; Williams, 1993; Geba, 2002), these evidences usually have some common problems:

1. Relatively short-term trials (usually around 4-6 weeks) (Courtney, 2002) – in order to find out the best long-term symptom controlling drug in OA, the long-term efficacy and toxicity of NSAIDs/Coxibs have not yet been

identified;

2. Elderly and patients with comorbid conditions such as cardiac and renal disease were usually excluded in these trials (Scott, 2004) – opposite to the practical situation of the OA patients and the adverse effects of NSAIDs/Coxibs on the elderly and patients with comorbid diseases and drug interaction.

Even the American College of Rheumatologist's guideline updated in 2000 (which suggested that NSAIDs could be used as initial pharmacological treatment for the patients with more severe OA pain, however, the method to reliably quantify the OA pain severity was not stated in the guideline.) was criticized on its completeness of the literature search, interpretation of available evidence, differentiation between opinion and evidence and the presence of unbalanced or biased recommendations (Lynch, 2001; Dart, 2001; Dieppe, 2001; Brandt, 2001).

In fact, NSAIDs give more pain relief to some patients with OA (the benefit is small) (Wegman, 2004), but others (almost half those studied) find acetaminophen either better than NSAIDs or equally effective (Wolfe, 2000), and there are no reliable clinical predictors of response to NSAIDs or acetaminophen (Bradley, 1992; Bradley, 2001) (even the signs of joint inflammation, such as joint line and soft tissue tenderness, synovial thickening, joint effusion). Therefore, base on the effectiveness, relatively less drug interaction and low toxicity profile of acetaminophen, it should be used as an initial pharmacological therapy for OA patients and can be used for long-term symptom control in OA. For those OA patients with joint inflammation, which is intermittent (Brooks, 2003), NSAIDs/Coxibs can be used as adjunctive treatment for anti-inflammation and strengthening the pain relieving power of acetaminophen (Seideman, 1993).

Acetaminophen should be used with caution in patients who have liver disease and those with a history of excessive alcohol consumption (Clissold, 1986; Schiodt, 1997; Whitcomb, 1994; Seifert, 1993). Likewise, few studies reported the regular use of paracetamol/acetaminophen was associated, in a dose-dependent manner, with an increased risk of chronic renal failure. However, patients without pre-existing renal disease who used paracetamol/acetaminophen had no risk of end-stage renal disease (Fored, 2001). Also, the Scientific Advisory Board of the American National Kidney Foundation recommends acetaminophen as the preferred analgesic in patients with renal impairment (Henrich, 1996). Although there have been rare studies suggesting acetaminophen has dose dependent GI toxicity (Garcia Rodriguez, 2001; Warner, 1999), the findings are counter to other epidemiological evidence that shows no GI risk from acetaminophen (Langman, 1994) and it has not been shown to cause gastroduodenal injury in human trials (Lanza, 1998). The drug may prolong the half-life of warfarin, so patients taking warfarin must have their INR (International normalized ratio) monitored closely and their warfarin dose adjusted is necessary (Hyiek, 1998).

Acetaminophen should be taken in divided doses, at regular intervals, with total daily dose not exceeding 4g (Grainger, 2004). Although a number of patients will have only limited therapeutic response, it is important to ascertain whether the patient has given the drug a fair trial before determining this management to be a failure. Intermittent use or inadequate daily doses should be followed with a several-week trial of paracetamol/acetaminophen of up to 4g/d (Bijlsma, 2002).

2) Topical agents (NSAIDs, Capsaicin, Methylsalicylate)

Topical treatment is appropriate for patients as an adjunct to simple analgesia, monotherapy for a single symptomatic joint, or for patients who cannot tolerate systemic therapy (Grainger, 2004). There is evidence for the efficacy and use of topical NSAIDs and capsaicin in the management of knee OA and these treatments have a good safety record (Jordan, 2003).

Topical diclofenac recorded significant benefit over placebo for pain relief (Grace, 1999; Dreiser, 1993). Comparing diclofenac gel with ketoprofen gel (Waikakul, 1997) and piroxicam gel with oral ibuprofen (Dickson, 1991) showed equal efficacy between treatments. Eltenac gel showed a significant improvement in pain relief only in those with severe knee OA (Sandelin, 1997; Ottilinger, 2001).

There is good evidence for capsaicin's efficacy in knee OA from an RCT, and it would appear its efficacy is maintained (Deal, 1991). While using topical capsaicin, a local burning sensation is common, but decreases with continued use. Patients must avoid inadvertently transferring the capsaicin to eyes or mucous membranes (Grainger, 2004).

Capsaicin cream should be applied to the symptomatic joint 4 times daily (American College of Rheumatology Subcommittee on Osteoarthritis Guidelines, 2000).

3) Non-selective NSAIDs and selective COX-2 inhibitors (Coxibs)

NSAIDs should be considered in patients unresponsive to acetaminophen. In

patients with an increased gastrointestinal risk, non-selective NSAIDs and effective gastro-protective agents or selective COX-2 inhibitors should be used (Jordan, 2003). The clinical circumstances that both NSAIDs and coxibs may be used:

1. Patients who have had an inadequate response to non-pharmacologic modalities and to maximum doses of acetaminophen; or
2. As adjunctive therapy for patients who wish to continue acetaminophen, with the hope that there will be a need for lower doses of the NSAIDs or coxibs because of the underlying analgesic activity of acetaminophen.

However, coxibs are the drug of choice in patients at high risk for developing GI toxicity or bleeding.

There is good evidence that non-selective NSAIDs and selective COX-2 inhibitors are more efficacious than placebo and acetaminophen (Jordan, 2003; Geba, 2002), and especially better for the patients with severe pain (compared with acetaminophen) (Tannenbaum, 2000; Geba, 2002). However, there is no consistent evidence suggesting that COX-2 inhibitors is better than NASIDS and one NSAID is superior to another NSAID in relieving pain (Watson, 2000; Gotzsche, 2000; Lisse, 2003; McKenna, 2002; Myllykangas-Luosujarvi, 2002; Makarowski, 2002).

Side effects and risk factors:

Increased risk of upper gastrointestinal adverse events – non-selective NSAIDs only

It was found that ibuprofen is the lowest risk NSAID and azapropazone the highest risk agent, and the risk of injury from NSAIDs is greater at higher doses. High dose ibuprofen (2.4 gm/day) may not be safer than those NSAIDs defined as being

intermediate risk – drugs such as diclofenac and naproxen (Eccles, 1998).

There has been speculation that COX-2 selective agents are more beneficial than non-selective NSAIDs, particularly in those at higher risk of adverse gastrointestinal side effects. An RCT comparing celecoxib and diclofenac showed no difference in relieving pain, but there were more gastrointestinal side effects with diclofenac than celecoxib (McKenna, 2001). On the other hand, according to a systematic review comparing the efficacy, tolerability and upper gastrointestinal safety of celecoxib and NSAIDs, the gastrointestinal safety of celecoxib was still consistent in the patients taking aspirin, although the reduction in the incidence of ulcers detected by endoscopy was lower (Deeks, 2002).

Risk factors of upper gastrointestinal tract complications include age ≥ 65, history of peptic ulcer disease or of upper gastrointestinal bleeding, comorbid medical conditions, concomitant use of oral corticosteroids or anticoagulants, and possibly, smoking and alcohol consumption (Gabriel, 1991; Simon, 1996; Lanza, 1998).

Increased risk of renal adverse events – both non-selective NSAIDs and coxibs

Although coxibs have clearly been shown to reduce GI morbidity compared with non-selective NSAIDs, both drugs act in a similar manner at the level of the kidney (Brater, 1999; Rossat, 1999; Whelton, 2000) and demonstrate a dose-dependent effect on blood pressure, and are associated with a small, but measurable, increase in the incidence of oedema (de Leeuw, 1996; Fierro-Carrion, 1997; Johnson, 1994; Pope, 1993; Ruoff, 1998; Whelton, 1999).

Risk factors of renal complications include having intrinsic renal disease (usually

defined as a serum creatinine level ≥ 2.0mg/dl), age ≥ 65, hypertension, congestive heart failure and concomitant use of diuretics and angiotensin-converting enzyme inhibitors (Garell, 1984).

Other increased risk – both non-selective NSAIDs and coxibs

Both non-selective NSAIDs and COX-2 inhibitors may cause acute deterioration in hypertension (The Australian COX-2-Specific Inhibitor (CSI) Prescribing Group, 2002). There is a recognized association between the use of NSAIDs and exacerbation of congestive heart failure (CHF). When using NSAIDs and coxibs in patients at high risk for developing CHF, it should be undertaken with caution (Heerdink, 1998; Page, 2000).

Other increased risk – coxibs only

Compared with patients using naproxen, those using rofecoxib[†] had a fourfold increase in the rate of myocardial infarction (Bombardier, 2000). And doses of rofecoxib of more than 25mg/day were associated with an excess risk of coronary events (Wayne, 2002; Whelton, 2002). Since rofecoxib is a highly selective COX-2 inhibitor, the inhibition of leukocyte COX-2 at a site of inflammation without inhibition of platelet COX-1 may lead to a prothrombotic state. Rofecoxib should be avoided in patients with known risk factors for cardiovascular disease. This risk is hypothesised to be especially high in patients with conventional cardiovascular risk factors (smoking, hypertension, diabetes mellitus, hyperlipidaemia and family history of premature cardiovascular disease in a first-degree relative) (Grainger, 2004). The

[†] Due to an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment in the patients taking VIOXX (rofecoxib) compared to those taking placebo in the APPROVe trial (a three-year, prospective, randomized, placebo-controlled clinical trial about preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas), Merck voluntarily withdrew VIOXX from the market on 30th Sept 2004.

use of celecoxib is contraindicated in patients with a history of an allergic reaction to a sulphonamide (Pope, 1993).

Usage

Patients with no risk factors should use non-selective NSAIDs, commencing at a low dose, with dose titration against effect. NSAIDs should be used on an as-required basis, although this often means continuous use (Heerdink, 1998). Those with the lowest risk profile for upper-gastrointestinal haemorrhage, ibuprofen and dicofenac are recommended (Jordan, 2003).

COX-2 inhibitors are recommended for patients with any gastrointestinal risk factors (Pope, 1993; Page, 2000). Rofecoxib should be avoided in patients with known risk factors for cardiovascular disease, and should never be prescribed at doses greater than 25mg daily (Grainger, 2004).

Patients prescribed non-selective NSAIDs and COX-2 inhibitors should be counselled about the symptoms of upper-gastrointestinal haemorrhage and monitored for new or severe upper-gastrointestinal symptoms. NSAIDs should never be used in combination, except with low-dose aspirin for cardioprotection (Heerdink, 1998).

For patients with any risk factors for deterioration in renal function, NSAIDs and COX-2 inhibitors should only be prescribed after very careful consideration of all other options. Plasma sodium, potassium and creatinine levels, blood pressure and the presence of oedema should be checked at baseline and regular intervals (Pope, 1993).

Alternative to coxibs

Misoprostol significantly reduced the risk of endoscopic ulcers. Standard doses of histamine-2 receptor antagonists effectively reduced the risk of endoscopic duodenal but not gastric ulcers. Double doses of histamine-2 receptor antagonists and proton pump inhibitors effectively reduced the risk of endoscopic duodenal and gastric ulcers, and were better tolerated than misprostol (Rostom, 2003).

4) SYSADOA

A) Hyaluronic Acid / Hyaluronan

There is evidence to support the efficacy of hyaluronic acid in the management of knee OA both for pain reduction (Dougados, 1993; Corrado, 1995; Huskisson, 1999; Carrabba, 1995; Tasciotaoglu, 2003) and functional improvement (Wobig, 1999), and it is more effective for the patients over 60 (Lohmander, 1996) or those with less severe disease, but less effective for those with effusion at baseline (Lussier, 1996). Its effect is significantly better than placebo (Karlsson, 2002) and comparable to oral NSAIDs (Altman, 1998; Adams, 1995; Kirwan, 1999) and intra-articular glucocorticoid injections (Kotz, 1999). However, although pain relief may be obtained for several months, rather than for several weeks as with steroid, this benefit may be offset by its slower onset of action and by its requirement of 3-5 weekly injections. There is minimal evidence for a role in disease modification (American College of Rheumatology Subcommittee on Osteoarthritis Guidelines, 2000).

Adverse effects are uncommon, but include acute joint pain with effusion, which

requires aspiration to exclude sepsis (Grainger, 2004).

B) Glucosamine Sulphate / Chondroitin Sulphate

These two SYSADOA demonstrated moderate to large effects on pain and disability in OA compared with placebo, they are also safe and associated with few side effects (McAlindon TE, 2000; Pavelka, 2002). Similar to other SYSADOA, they have both symptomatic effects and may modify structure, especially for those with less severe radiographic knee OA (Bruyere, 2003).

Since both drugs had slow onset of action, they were less effective than the NSAIDs (chondroitin sulphate vs. diclofenac, glucosamine sulphate vs. ibuprofen) in short period of time, but their effect could last longer than the NSAIDs (Morreale, 1996; Vaz, 1982). The efficacy of glucosamine and chondroitin sulphate in combination was significant in those with mild to moderate knee OA, but had no improvement over placebo in those with severe disease (Das, 2000).

Glucosamine sulphate showed delayed progression of joint space loss and improvement in pain and function scores as compared with placebo (Reginster, 2001). It is contraindicated in seafood allergy, but is otherwise well tolerated and causes no major side effects (Grainger, 2004).

Glucosamine sulphate should be used at a dose of 1500mg per day as a divided dose for at least 3 months to determine whether it is therapeutic in any given patient (Grainger, 2004).

C) Diacerein / Diacetylrhein

Diacerein has symptomatic effects and may modify structure. Compared with placebo, diacerein had significant differences in pain and handicap scores at doses of 100mg/day, but a significant number of adverse events were seen at high doses (American College of Rheumatology Subcommittee on Osteoarthritis Guidelines, 2000). Compared to diclofenac and NSAID, it is similar to glucosamine and chondroitin sulphate and also suffers from slow onset of action, but long lasting of effect (Lequesne, 1998). The delayed onset of action has to be clearly explained to, and understood by, patients. Otherwise, it will result in discontinuation of the drug because of inefficacy after a few days (Hochberg, 2001).

5) <u>Intra-articular corticosteroids</u>

Intra-articular injections of corticosteroid are effective, particularly for the patients who have signs of local inflammation with a joint effusion, but give relatively short-lived benefit (Gaffney, 1995). Injection can be used as monotherapy in selected patients or as an adjunct to systemic therapy with an analgesic, a non-selective NSAID, or a COX-2-specific inhibitor.

When joints are painful and swollen, aspiration of fluid followed by intra-articular injection of glucocorticoid preparation (e.g. up to 40mg triamcinolone hexacetonide) is an effective shot-term method of decreasing pain and increasing quadriceps strength (Kirwan, 1997; Creamer, 1997). The effect of repeated injections is not particularly effective in reducing pain, but safe (Raynauld, 2003). It is wise to give injection in specific joint no more than every 3 to 4 months.

Iatrogenic infection is rare if aseptic technique is used. Common side effects include flushing, worsening hyperglycemia and post-injection flare of synovitis due to a reaction to the crystalline steroid suspensions, but the flares are temporary and can be treated with analgesics and cold compresses.

6) <u>Opioids</u>

Opioid analgesics, with or without acetaminophen, are useful alternatives in patients in whom NSAIDs, including COX-2 selective inhibitors, are contraindicated, ineffective, and/or poorly tolerated (Silverfield, 2002; Emkey, 2004). The efficacy of tramadol has been found to be comparable with that of ibuprofen in patients with hip and knee OA (Dalgin, 1997). A RCT showed that treatment of knee OA with tramadol allowed reduction of naproxen dose among those patients with naproxen-responsive pain (Schnitzer, 1999).

The combination of codeine and acetaminophen provides better analgesia than acetaminophen alone. For patients with the acute pain in hip or knee OA, no difference in analgesic efficacy was demonstrated between combinations of acetaminophen with either dextropropoxyphene or codeine, but the combination with dextropropoxyphene was significantly better tolerated (Boissier, 1992).

Mean effective daily doses of tramadol have generally been in the range of 200-300mg, given in 4 divided doses (American College of Rheumatology Subcommittee on Osteoarthritis Guidelines, 2000).

Tolerance, dependence, and adverse effects, including respiratory depression and constipation, may occur with opioid usage. Side effects of tramadol are common and include nausea, constipation and drowsiness and it is contraindicated in seizure disorders, as it lowers the seizure threshold, and used in combination with selective serotonin reuptake inhibitors because of the risk of serotoninergic syndrome (Grainger, 2004). Nausea, vomiting, dizziness and constipation are the side effects of the combination of codeine and acetaminophen (Kjaersgaard-Andersen, 1990).

IV) Recommendations

- Management of OA has to be individualized, holistic, and patient-centred, taking into account of factors such as patient's beliefs, co morbid disease and activity requirements etc. (IV, D)
- Nonpharmacologic interventions should form an integral part of the treatment of OA but the optimal treatment requires combination with pharmacologic measures. (Ia, A)
- Acetaminophen / paracetamol should be tried first in patients who have mild to moderate pain and is as effective as NSAIDs. For those OA patients with joint inflammation, which is intermittent, NSAIDs/Coxibs can be used as adjunctive treatment for anti-inflammation and to strengthen the pain relieving power of acetaminophen. Acetaminophen should be used with caution in patients with liver disease and monitered closely in those taking warfarin. (Ia, A)
- NSAIDs are more efficacious than acetaminophen / paracetamol in some patients, particularly those who experience severe pain. The addition of a gastroprotective agent to a conventional NSAID is required for those with an increased risk of gastrointestinal complications. (Ia, A)
- Cyclo-oxygenase-2 (COX-2) inhibitors are superior to placebo with a lower incidence of gastrointestinal side effects. However, as with non-selective NSAIDs, caution should be exercised in patients who have renal impairment. Coxibs should be avoided in patients with known risk factors for cardiovascular disease, the risk is especially high in patients with conventional cardiovascular risk factors (smoking, hypertension, diabetes mellitus, hyperlipidaemia and family history of premature cardiovascular disease in a

first-degree relative) (Ia, A)

- The use of topical therapy might be beneficial, especially for the patients who are unable or unwilling to take oral NSAIDs. (Ib, A)
- Intra-articular corticosteroid injections provide short-term relief of acute knee pain, though neither the presence of effusion nor any other clinical feature examined predicted the response to injection. (Ia, A)
- Symptomatic slow acting drugs for osteoarthritis (SYSADOA) (including glucosamine sulphate, chondroitin sulphate, diacerein and hyaluronic acid) are probably effective in OA with a slow onset of action, especially glucosamine sulphate and chondroitin sulphate. They may also modify the structure in knee OA. (Ib, A)
- Opioid analgesics, with or without acetaminophen, are useful for the treatment of moderate to severe pain in patients who are intolerant of or unresponsive to nonselective NSAIDs or COX-2 inhibitors. Side effects are common and include nausea, constipation and drowsiness, and they are contraindicated in seizure disorders. (Ib, A)

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Appendix I

Guidelines for the treatment of hip and / or knee osteoarthritis

Authors	Title	Source
Hochberg MC. Dougados M.	Pharmacological therapy of osteoarthritis	Baillieres Best Pract Res Clin Rheumatol. 15(4):583-93, 2001 Oct.
Brighton S. Mody GM. Tikly M. et al.	Osteoarthritis: clinical guideline 2003.	S Afr Med J. 93(12 Pt 2):972-90, 2003 Dec.
M Dougados et al.	EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT).	Ann Rheum Dis. 62(12):1145-55, 2003 Dec.
Grainger R. Cicuttini FM.	Medical Management of Osteoarthritis of the knee and hip joints	Med J Aust. 180(5):232-6, 2004 Mar 1.
American College of Rheumatology	Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines.	Arthritis Rheum. 43(9):1905-15, 2000 Sep.
Eccles M. Freemantle N. Mason J.	North of England evidence based guideline development project: summary guideline for non-steroidal anti-inflammatory drugs versus basic analgesia in treating the pain of degenerative arthritis	BMJ. 317(7157):526-30, 1998 Aug 22.
The Australian COX-2-Specific Inhibitor (CSI) Prescribing Group	Considerations for the safe prescribing and use of COX-2-specific inhibitors	Med J Aust. 176(7):328-31, 2002 Apr 1.
National Institute for Clinical Excellence (NICE)	Technology Appraisal Guidance No. 27. Guidance on the use of cyclo-oxygenase (COX) II selective inhibitors, celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis	NICE 2001/ 025 Issued: 26 July 2001
Schnitzer TJ. American College of Rheumatology.	Update of ACR guidelines for osteoarthritis: role of the coxibs.	J Pain Symptom Manage. 23(4 Suppl):S24-30; discussion S31-4, 2002 Apr.
Tannenbaum H. Peloso PM. Russell AS. et al.	An evidence-based approach to prescribing NSAIDs in the treatment of osteoarthritis and rheumatoid arthritis: The Second Canadian Consensus Conference.	Can J Clin Pharmacol. 7 Suppl A:4A-16A, 2000 Autumn.
Scott DL.	Guidelines for the diagnosis, investigation and management of osteoarthritis of the hip and knee. Report of a Joint Working Group of the British Society for Rheumatology and the Research Unit of the Royal College of Physicians	J R Coll Physicians Lond. 27(4):391-6, 1993 Oct.
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Scott DL. Shipley M. Dawson A. et al.	The clinical management of rheumatoid arthritis and osteoarthritis: strategies for improving clinical effectiveness	Br J Rheumatol. 37(5):546-54, 1998 May
Vallerand AH.	Treating osteoarthritis pain	Nurse Pract. 28(4):7-15; quiz 16-7, 2003 Apr.
Lane NE, Thompson JM	Management of osteoarthritis in the primary-care setting: an evidence-based approach to treatment	Am J Med. 103(6A):25S-30S, 1997 Dec 29.
Bijlsma JW.	Analgesia and the patient with osteoarthritis	Am J Ther. 9(3):189-97, 2002 May-Jun.
Fitzgerald GK. Oatis C.	Role of physical therapy in management of knee osteoarthritis	Curr Opin Rheumatol. 16(2):143-7, 2004 Mar.
Bischoff HA. Roos EM.	Effectiveness and safety of strengthening, aerobic, and coordination exercises for patients with osteoarthritis	Curr Opin Rheumatol. 15(2):141-4, 2003 Mar.
Sharma L.	Nonpharmacologic management of osteoarthritis	Curr Opin Rheumatol. 14(5):603-7, 2002 Sep.
Cote LG.	Management of osteoarthritis	J Am Acad Nurse Pract. 13(11):495-501, 2001 Nov.

Authors	Title	Source
Baker K. McAlindon T.	Exercise for knee osteoarthritis	Curr Opin Rheumatol. 12(5):456-63, 2000 Sep.
Creamer P.	Osteoarthritis pain and its treatment	Curr Opin Rheumatol. 12(5):450-5, 2000 Sep.
Brandt KD.	The importance of nonpharmacologic approaches in management of osteoarthritis	Am J Med. 105(1B):39S-44S, 1998 Jul 27.
Hill J.	Patient education in rheumatic disease	Nurs Stand. 9(25):25-8, 1995 Mar 15-21.
Anonymous.	Work group recommendations: 2002 Exercise and Physical Activity Conference, St. Louis, Missouri. Session V: evidence of benefit of exercise and physical activity in arthritis	Arthritis Rheum. 49(3):453-4, 2003 Jun 15.
Baird CL.	First-line treatment for osteoarthritis. Part 2: Nonpharmacologic interventions and evaluation	Orthop Nurs. 20(6):13-8; quiz 18-20, 2001 Nov-Dec.

Appendix II

Systematic reviews / meta-analysis for the treatment of hip and / or knee osteoarthritis

Group	Drug	Authors	Title	Source
Acetaminophen / Paracetamol	Acetaminophen / Paracetamol	Towheed TE. Judd MJ. Hochberg MC. et al.	Acetaminophen for osteoarthritis.	Cochrane Database Syst Rev. (2):CD004257, 2003.
	Acetaminophen / Paracetamol	Brandt K.	Le paracetamol dans le traitement des douleurs arthrosiques. [Paracetamol in the treatment of osteoarthritis pain]. [French]	Drugs. 63 Spec No 2:23-41, 2003.
	Acetaminophen / NSAIDs	Wegman A. van der Windt D. van Tulder M. et al.	Nonsteroidal antiinflammatory drugs or acetaminophen for osteoarthritis of the hip or knee? A systematic review of evidence and guidelines.	J Rheumatol. 31(2):344-54, 2004 Feb.
Non-selective NSAIDs	Etodolac	Porzio F.	Meta-analysis of three double-blind comparative trials with sustained-release etodolac in the treatment of osteoarthritis of the knee.	Rheumatol Int. 13(2 Suppl):S19-24, 1993.
	Ibuprofen	Haase W. Fischer M.	Statistische Metaanalyse von multizentrischen klinischen Studien mit Ibuprofen im Hinblick auf die Kohortengrosse. [Statistical meta-analysis of multicenter clinical studies of ibuprofen with regard to cohort size]. [German]	Z Rheumatol. 50 Suppl 1:77-83, 1991.
	No Specific	Watson MC. Brookes ST. Kirwan JR. et al.	Non-aspirin, non-steroidal anti-inflammatory drugs for osteoarthritis of the knee.	Cochrane Database Syst Rev. (2):CD000142, 2000.
	No Specific	Towheed T. Shea B. Wells G. et al.	Analgesia and non-aspirin, non-steroidal anti-inflammatory drugs for osteoarthritis of the hip.	Cochrane Database Syst Rev. (2):CD000517, 2000.
	No Specific	Uemura S. Ochi T. Sugano K. et al.	Systematic review for evaluation of tolerability of nonsteroidal antiinflammatory drugs in osteoarthritis patients in Japan.	J Orthop Sci. 8(3):279-87, 2003.
	Tenoxicam, Piroxicam, Diclofenac, Indomethacin	Riedemann PJ. Bersinic S. Cuddy LJ. et al.	A study to determine the efficacy and safety of tenoxicam versus piroxicam, diclofenac and indomethacin in patients with osteoarthritis: a meta-analysis.	J Rheumatol. 20(12):2095-103, 1993 Dec.
	Diclofenac, Aspirin	Furst DE. Anderson W.	Differential effects of diclofenac and aspirin on serum glutamic oxaloacetic transaminase elevations in patients with rheumatoid arthritis and osteoarthritis.	Arthritis Rheum. 36(6):804-10, 1993 Jun.
COX-2 NSAIDs	Celecoxib	Deeks JJ. Smith LA. Bradley MD.	Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials.	BMJ. 325(7365):619, 2002 Sep 21.
	Celecoxib	Silverstein FE. Faich G. Goldstein JL. et al.	Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study.	JAMA. 284(10):1247-55, 2000 Sep 13.
	Celecoxib	Ashcroft DM. Chapman SR. Clark WK. et al.	Upper gastroduodenal ulceration in arthritis patients treated with celecoxib.	Ann Pharmacother. 35(7-8):829-34, 2001 Jul-Aug.
	No Specific	Schoenfeld P.	An evidence-based approach to the gastrointestinal safety profile of COX-2-selective anti-inflammatories.	Gastroenterol Clin North Am. 30(4):1027-44, viii-ix, 2001 Dec.
SYSADOA	Chondroitin Sulphate	Leeb BF. Schweitzer H. Montag K. Smolen JS.	A metaanalysis of chondroitin sulfate in the treatment of osteoarthritis.	J Rheumatol. 27(1):205-11, 2000 Jan.
	Glucosamine Sulphate	Towheed TE. Anastassiades TP. Shea B. et al.	Glucosamine therapy for treating osteoarthritis.	Cochrane Database Syst Rev. (1):CD002946, 2001.
	Glucosamine Sulphate	Matheson AJ. Perry CM.	Glucosamine: a review of its use in the management of osteoarthritis.	Drugs Aging. 20(14):1041-60, 2003.
	Hyaluronic Acid / Hyaluronan	Lo GH. LaValley M. McAlindon T. et al.	Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis.	JAMA. 290(23):3115-21, 2003 Dec 17.
	Hyaluronic Acid / Hyaluronan	Espallargues M. Pons JM.	Efficacy and safety of viscosupplementation with Hylan G-F 20 for the treatment of knee osteoarthritis: a systematic review.	Int J Technol Assess Health Care. 19(1):41-56, 2003 Winter.
	Hyaluronic Acid / Hyaluronan	Aggarwal A. Sempowski IP.	Hyaluronic acid injections for knee osteoarthritis. Systematic review of the literature.	Can Fam Physician. 50:249-56, 2004 Feb.
	Hyaluronic Acid / Hyaluronan	Wen DY.	Intra-articular hyaluronic acid injections for knee osteoarthritis.	Am Fam Physician. 62(3):565-70, 572, 2000 Aug 1.

Group	Drug	Authors	Title	Source
	Hyaluronic Acid / Hyaluronan	Wang CT. Lin J. Chang CJ. et al.	Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials.	J Bone Joint Surg Am. 86-A(3):538-45, 2004 Mar.
	Avocado-soybean Unsaponifiables (ASU)	Ernst E.	Avocado-soybean unsaponifiables (ASU) for osteoarthritis - a systematic review.	Clin Rheumatol. 22(4-5):285-8, 2003 Oct.
	No Specific	Bellamy N. Campbell J. Wells G et al.	Viscosupplementation for osteoarthritis of the knee	Cochrane Database Syst Rev. Protocol
	Glucosamine / Chondroitin Sulphate	Richy F. Bruyere O. Ethgen O. et al.	Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis.	Arch Intern Med. 163(13):1514-22, 2003 Jul 14.
	Glucosamine / Chondroitin Sulphate	McAlindon TE. LaValley MP. Gulin JP. et al.	Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis.	JAMA. 283(11):1469-75, 2000 Mar 15.
IA Steroids	IA Steroids	Bellamy N. Campbell J. Wells G. et al.	Intra-articular corticosteroids for osteoarthritis of the knee	Cochrane Database Syst Rev. Protocol
	IA Steroids	Godwin M. Dawes M.	Intra-articular steroid injections for painful knees. Systematic review with meta-analysis.	Can Fam Physician. 50:241-8, 2004 Feb.
	IA Steroids	Arroll B. Goodyear-Smith F.	Corticosteroid injections for osteoarthritis of the knee: meta-analysis.	BMJ. 328(7444):869, 2004 Apr 10.
Opioids	Opioids	Husni E. Welch V. Simon L. et al.	Opioid therapy for treating osteoarthritis pain	Cochrane Database Syst Rev. Protocol
No Specific Drugs	No Specific	Towheed TE. Hochberg MC.	A systematic review of randomized controlled trials of pharmacological therapy in osteoarthritis of the hip.	J Rheumatol. 24(2):349-57, 1997 Feb.
	No Specific	Towheed TE. Hochberg MC.	A systematic review of randomized controlled trials of pharmacological therapy in osteoarthritis of the knee, with an emphasis on trial methodology.	Semin Arthritis Rheum. 26(5):755-70, 1997 Apr.
Others	Non-pharmacologic	Superio-Cabuslay E. Ward MM. Lorig KR.	Patient education interventions in osteoarthritis and rheumatoid arthritis: a meta-analytic comparison with nonsteroidal antiinflammatory drug treatment.	Arthritis Care & Research. 9(4):292-301, 1996 Aug.
	Non-pharmacologic	Brosseau L. Yonge KA. Robinson V. et al.	Thermotherapy for treatment of osteoarthritis	Cochrane Database Syst Rev. (4):CD004522, 2003.
	Non-pharmacologic	Fransen M. McConnell S. Bell M.	Exercise for osteoarthritis of the hip or knee	Cochrane Database Syst Rev. (3):CD004286, 2003.
	Non-pharmacologic	Brosseau L. MacLeay L. Robinson V. et al.	Intensity of exercise for the treatment of osteoarthritis	Cochrane Database Syst Rev. (2):CD004259, 2003.
	Non-pharmacologic	Fransen M. McConnell S. Bell M.	Therapeutic exercise for people with osteoarthritis of the hip or knee. A systematic review	J Rheumatol. 29(8):1737-45, 2002 Aug.
	Non-pharmacologic	van Baar ME. Assendelft WJ. Dekker J. et al.	Effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a systematic review of randomized clinical trials	Arthritis Rheum. 42(7):1361-9, 1999 Jul.
	Non-pharmacologic	Ernst E.	Acupuncture as a symptomatic treatment of osteoarthritis. A systematic review.	Scand J Rheumatol. 26(6):444-7, 1997.

Appendix III

Randomised controlled trials / control trials for the treatment of hip and / or knee osteoarthritis

Authors	Title	Source
Adler L. McDonald C. O'Brien C. Wilson M.	A comparison of once-daily tramadol with normal release tramadol in the treatment of pain in osteoarthritis.	J Rheumatol. 29(10):2196-9, 2002 Oct.
Bacon TH. Hole JG. North M. Burnett I.	Analgesic efficacy of sustained release paracetamol in patients with osteoarthritis of the knee.	Brit J Clin Pharmaco. 53(6):629-36, 2002 Jun.
Bianchi M. Broggini M.	A randomised, double-blind, clinical trial comparing the efficacy of nimesulide, celecoxib and rofecoxib in osteoarthritis of the knee.	Drugs. 63 Suppl 1:37-46, 2003.
Bruhlmann P. Michel BA.	Topical diclofenac patch in patients with knee osteoarthritis: a randomized, double-blind, controlled clinical trial.	Clin Exp Rheumatol. 21(2):193-8, 2003 Mar-Apr.
Bruyere O. Honore A. Ethgen O. Rovati LC. Giacovelli G. Henrotin YE. Seidel L. Reginster JY.	Correlation between radiographic severity of knee osteoarthritis and future disease progression. Results from a 3-year prospective, placebo-controlled study evaluating the effect of glucosamine sulfate.	Osteoarthritis Cartilage. 11(1):1-5, 2003 Jan.
Caldwell JR. Rapoport RJ. et al.	Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial.	J Pain Symptom Manage. 23(4):278-91, 2002 Apr.
Case JP. Baliunas AJ. Block JA.	Lack of efficacy of acetaminophen in treating symptomatic knee osteoarthritis: a randomized, double-blind, placebo-controlled comparison trial with diclofenac sodium.	Arch Intern Med. 163(2):169-78, 2003 Jan 27.
Cohen M. Wolfe R. Mai T. Lewis D.	A randomized, double blind, placebo controlled trial of a topical cream containing glucosamine sulfate, chondroitin sulfate, and camphor for osteoarthritis of the knee.	J Rheumatol. 30(3):523-8, 2003 Mar.
Emkey R. Rosenthal N. Wu SC. Jordan D. Kamin M. CAPSS-114 Study Group.	Efficacy and safety of tramadol/acetaminophen tablets (Ultracet) as add-on therapy for osteoarthritis pain in subjects receiving a COX-2 nonsteroidal antiinflammatory drug: a multicenter, randomized, double-blind, placebo-controlled trial.	J Rheumatol. 31(1):150-6, 2004 Jan.
Fioravanti A. Storri L. Di Martino S. Bisogno S. Oldani V. Scotti A. Marcolongo R.	A randomized, double-blind, multicenter trial of nimesulide-beta-cyclodextrin versus naproxen in patients with osteoarthritis.	Clin Ther. 24(4):504-19, 2002 Apr.
Geba GP. Weaver AL. et al.	Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee: a randomized trial.	JAMA. 287(1):64-71, 2002 Jan 2.
Gibofsky A. Williams GW. McKenna F. Fort JG.	Comparing the efficacy of cyclooxygenase 2-specific inhibitors in treating osteoarthritis: appropriate trial design considerations and results of a randomized, placebo-controlled trial.	Arthritis Rheum. 48(11):3102-11, 2003 Nov.
Goldstein JL. Kivitz AJ. Verburg KM. Recker DP. Palmer RC. Kent JD.	A comparison of the upper gastrointestinal mucosal effects of valdecoxib, naproxen and placebo in healthy elderly subjects.	Aliment Pharm Therap. 18(1):125-32, 2003 Jul 1.
Gottesdiener K. Schnitzer T. et al.	Results of a randomized, dose-ranging trial of etoricoxib in patients with osteoarthritis.	Rheumatology. 41(9):1052-61, 2002 Sep.
Herrera JA. Gonzalez M.	Comparative evaluation of the effectiveness and tolerability of nimesulide versus rofecoxib taken once a day in the treatment of patients with knee osteoarthritis.	Am J Ther. 10(6):468-72, 2003 Nov-Dec.
Hughes R. Carr A.	A randomized, double-blind, placebo-controlled trial of glucosamine sulphate as an analgesic in osteoarthritis of the knee.	Rheumatology. 41(3):279-84, 2002 Mar.
Hunt RH. Harper S. Callegari P. Yu C. Quan H. Evans J. James C. Bowen B. Rashid F.	Complementary studies of the gastrointestinal safety of the cyclo-oxygenase-2-selective inhibitor etoricoxib.	Aliment Pharm Therap. 17(2):201-10, 2003 Jan.
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Jagtap SA. Lahoti S. Anwaruddin K. Ram S. Ballary C. Desai A.	Evaluation of efficacy, safety and tolerability of valdecoxib in osteo-arthritis patients--an Indian study.	J Indian Med Assoc. 100(11):673-4, 2002 Nov.
Karlsson J. Sjogren LS. Lohmander LS.	Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study.	Rheumatology. 41(11):1240-8, 2002 Nov.
Kivitz A. Eisen G. Zhao WW. Bevirt T. Recker DP.	Randomized placebo-controlled trial comparing efficacy and safety of valdecoxib with naproxen in patients with osteoarthritis.	J Fam Practuce. 51(6):530-7, 2002 Jun.
Leopold SS. Redd BB. Warme WJ. Wehrle PA. Pettis PD. Shott S.	Corticosteroid compared with hyaluronic acid injections for the treatment of osteoarthritis of the knee. A prospective, randomized trial.	J Bone Joint Surg Am. 85-A(7):1197-203, 2003 Jul.
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Leung AT. Malmstrom K. et al.	Efficacy and tolerability profile of etoricoxib in patients with osteoarthritis: A randomized, double-blind, placebo and active-comparator controlled 12-week efficacy trial.	Curr Med Res Opin. 18(2):49-58, 2002.
Liang TH. Hsu PN.	Double-blind, randomised, comparative trial of etodolac SR versus diclofenac in the treatment of osteoarthritis of the knee.	Curr Med Res Opin. 19(4):336-41, 2003.
Lisse JR. Perlman M. et al.	Gastrointestinal tolerability and effectiveness of rofecoxib versus naproxen in the treatment of osteoarthritis: a randomized, controlled trial.	Ann Intern Med. 139(7):539-46, 2003 Oct 7.
Makarowski W. Zhao WW. Bevirt T. Recker DP.	Efficacy and safety of the COX-2 specific inhibitor valdecoxib in the management of osteoarthritis of the hip: a randomized, double-blind, placebo-controlled comparison with naproxen.	Osteoarthritis Cartilage. 10(4):290-6, 2002 Apr.
McKenna F. Arguelles L. Burke T. Lefkowith J. Geis GS.	Upper gastrointestinal tolerability of celecoxib compared with diclofenac in the treatment of osteoarthritis and rheumatoid arthritis.	Clin Exp Rheumatol. 20(1):35-43, 2002 Jan-Feb.
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Myllykangas-Luosujarvi R. Lu HS. et al.	Comparison of low-dose rofecoxib versus 1000 mg naproxen in patients with osteoarthritis. Results of two randomized treatment trals of six weeks duration.	Scand J Rheumatol. 31(6):337-44, 2002.
Pavelka K. Gatterova J. Olejarova M. Machacek S. Giacovelli G. Rovati LC.	Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study.	Arch Intern Med. 162(18):2113-23, 2002 Oct 14.
Petrella RJ. DiSilvestro MD. Hildebrand C.	Effects of hyaluronate sodium on pain and physical functioning in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled clinical trial.	Arch Intern Med. 162(3):292-8, 2002 Feb 11.
Raynauld JP. Buckland-Wright C. et al.	Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial.	Arthritis Rheum. 48(2):370-7, 2003 Feb.
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Tasciotaoglu F. Oner C.	Efficacy of intra-articular sodium hyaluronate in the treatment of knee osteoarthritis.	Clin Rheumatol. 22(2):112-7, 2003 May.
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Ng MM. Leung MC. Poon DM.	The effects of electro-acupuncture and transcutaneous electrical nerve stimulation on patients with painful osteoarthritic knees: a randomized controlled trial with follow-up evaluation.	J Altern Complement Med. 9(5):641-9, 2003 Oct.
Foley A. Halbert J. Hewitt T. Crotty M.	Does hydrotherapy improve strength and physical function in patients with osteoarthritis--a randomised controlled trial comparing a gym based and a hydrotherapy based strengthening programme.	Ann Rheum Dis. 62(12):1162-7, 2003 Dec.
Dias RC. Dias JM. Ramos LR.	Impact of an exercise and walking protocol on quality of life for elderly people with OA of the knee.	Physiother Res Int. 8(3):121-30, 2003.
Song R. Lee EO. Lam P. Bae SC.	Effects of tai chi exercise on pain, balance, muscle strength, and perceived difficulties in physical functioning in older women with osteoarthritis: a randomized clinical trial.	J Rheumatol. 30(9):2039-44, 2003 Sep.
Huang MH. Lin YS. Yang RC. Lee CL.	A comparison of various therapeutic exercises on the functional status of patients with knee osteoarthritis.	Semin Arthritis Rheum. 32(6):398-406, 2003 Jun.
Quilty B. Tucker M. Campbell R. Dieppe P.	Physiotherapy, including quadriceps exercises and patellar taping, for knee osteoarthritis with predominant patello-femoral joint involvement: randomized controlled trial.	J Rheumatol. 30(6):1311-7, 2003 Jun.
Cheing GL. Hui-Chan CW. Chan KM.	Does four weeks of TENS and/or isometric exercise produce cumulative reduction of osteoarthritic knee pain?.	Clin Rehabil. 16(7):749-60, 2002 Nov.
Thomas KS. Muir KR. Doherty M. Jones AC. O'Reilly SC. Bassey EJ.	Home based exercise programme for knee pain and knee osteoarthritis: randomised controlled trial.	BMJ. 325(7367):752, 2002 Oct 5.

Belza B. Topolski T. Kinne S. Patrick DL. Ramsey SD.	Does adherence make a difference? Results from a community-based aquatic exercise program.	Nurs Res. 51(5):285-91, 2002 Sep-Oct.
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