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

Guideline Development Panel
Professor Albert Lee, Department of Community and Family Medicine, CUHK
Dr Clement Tsang, Department of Community and Family Medicine, CUHK
Professor William Wong, Department of Community and Family Medicine, CUHK
Professor Samuel Wong, Department of Community and Family Medicine, CUHK

Guideline Review Panel
Professor K.M. Chan, Chair Professor, Department of Orthopaedics and Traumatology, CUHK
Dr Timothy C.Y. Kwok, Associate Professor, Division of Geriatrics, Department of Medicine and Therapeutics, CUHK
Professor Kenneth K.C. Lee, Professor, School of Pharmacy, CUHK
Dr K.Y. Lee, Chief Hospital Manager and Specialist in Rheumatology, Union Hospital
Dr Arran Leung, part-time Assistant Professor (Physiotherapist), Centre for Health Education and Health Promotion, CUHK
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).

<table>
<thead>
<tr>
<th>Categories of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia  _Evidence from meta-analysis of randomised controlled trials</td>
</tr>
<tr>
<td>Ib  _Evidence from at least one randomised controlled trial</td>
</tr>
<tr>
<td>IIa _Evidence from at least one controlled study without randomisation</td>
</tr>
<tr>
<td>IIb _Evidence from at least one other type of quasi-experimental study</td>
</tr>
<tr>
<td>III _Evidence from descriptive studies, such as comparative studies, correlation studies and case-control studies</td>
</tr>
<tr>
<td>IV  _Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A_Directly based on category I evidence</td>
</tr>
<tr>
<td>B_Directly based on category II evidence or extrapolated recommendation from category I evidence</td>
</tr>
<tr>
<td>C_Directly based on category III evidence or extrapolated recommendation from category I or II evidence</td>
</tr>
<tr>
<td>D_Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence</td>
</tr>
</tbody>
</table>
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) **Exercise / Physiotherapy**

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-inflammatory 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 if 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 $\geq 2.0\text{mg/dl}$, age $\geq 65$, 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 diclofenac 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 misoprostol (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) Intra-articular corticosteroids

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) Opioids

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 monitored 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
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)
References


Fierro-Carrion GA, Ram CVS. (1997) Nonsteroidal antiinflammatory drugs (NSAIDs) and blood pressure. Am J Cardiol 80: 775–776.


### Appendix I

#### Guidelines for the treatment of hip and/or knee osteoarthritis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Title</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authors</td>
<td>Title</td>
<td>Source</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>McAlindon T.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix II

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
<th>Authors</th>
<th>Title</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Forst DE. Anderson W.</td>
<td>Differential effects of diclofenac and aspirin on serum glutamic oxaloacetic transaminase elevations in patients with rheumatoid arthritis and osteoarthritis.</td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>Drug</td>
<td>Authors</td>
<td>Title</td>
<td>Source</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
## Appendix III

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

<table>
<thead>
<tr>
<th>Authors</th>
<th>Title</th>
<th>Source</th>
</tr>
</thead>
</table>


Song R. Lee EO. Larn 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. 2003;30(9):2039-44.


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. 2002;16(7):749-60.

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title</th>
<th>Journal</th>
<th>Publication Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evcil D. Sonel B.</td>
<td>Effectiveness of a home-based exercise therapy and walking program on osteoarthritis of the knee.</td>
<td>Rheumatol Int. 22(3):103-6, 2002 Jul.</td>
<td></td>
</tr>
</tbody>
</table>