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## Management of Osteoarthritis in Older People

Richard H Osborne, Adam B Chapman, Geoffrey J McColl

### ABSTRACT

Osteoarthritis is a common cause of disability in the elderly. Management involves pharmacological and non-pharmacological therapies, often in combination. Paracetamol is regarded as the drug of first choice in the management of pain, however anti-inflammatory drugs or other analgesics should be considered if regular paracetamol fails. If conventional non-steroidal anti-inflammatory drugs or cyclo-oxygenase-2 specific inhibitors are prescribed, attention should be paid to gastrointestinal, hepatic, cardiac and renal risk factors. Recent research indicates that some complementary and alternative medicines (e.g. glucosamine) are effective and should be considered, particularly given their low side effect profile. The evidence around surgical procedures mostly supports arthroplasty (joint replacement) for severe, refractory knee osteoarthritis; however arthroscopy has generally been found to be ineffective. Physical therapies, weight loss and joint protection also have a place in management and given that osteoarthritis contributes to psychological morbidity, supportive programs such as the Arthritis Self-Management Course should also be routinely recommended.

**J Pharm Pract Res 2002; 32: 276-281.**

### INTRODUCTION

Osteoarthritis (OA) is a slowly progressive, degenerative condition characterised by abnormalities in articular cartilage; subchondral bone; synovial membrane and fluid; and periarticular muscles, tendons and bursa. The prevalence of the condition greatly increases with age.<sup>1-3</sup> The coexistence of OA with other age-related conditions may amplify the disability of the arthritis, as well as posing specific problems in the implementation of effective and safe therapies.

In population surveys of Australians over 50 years of age, 41% report having arthritis (19% state OA, 7% rheumatoid arthritis and 15% arthritis 'not specified').<sup>4</sup> In a community-based survey in Sydney, arthritis or rheumatism was the leading self-reported chronic condition reported by 60%, 56% and 60% of women and 41%, 47% and 44% of men in three age groups (65-74, 75-84 and >85 years) respectively.<sup>5</sup> In the Victorian Burden of Disease Study, in women aged 55 and over, dementia was the highest contributor to prevalent years of life lost due to disability, and OA was the second.<sup>6</sup>

Despite the high prevalence of OA, the risk factors have been poorly studied. Epidemiological studies have identified some risk factors, particularly obesity, physical inactivity, occupation/recreational injury and genetic factors.<sup>7</sup> The factors that determine progression of OA have also been poorly documented, but injury and obesity appear to be the most important, particularly for progression of OA of the knee.<sup>8,9</sup>

The treatment of OA in the elderly is essentially the same as in younger patients and follows the guidelines of the American College of Rheumatology.<sup>10</sup> However potential co-morbidities which come with increasing age must be taken into account when treatment options are selected. The implementation of non-pharmacological therapies is highly recommended as toxicity from many pharmacological therapies in the elderly is unacceptably increased.

### NON-PHARMACOLOGICAL THERAPIES

#### Self-Management

The Arthritis Self-Management Course and the Chronic Disease Self-Management Program are community-based programs that are designed to help people achieve a better quality of life, and manage their health more effectively. They consist of six 'workshops' of two-and-a-half hours duration held over six weeks. Topics include: 'How to manage pain and fatigue', 'The benefits of physical activity', 'Understanding medication usage', 'Managing anger, fear and frustration', 'Solving health-related problems', and 'Better communication with doctors'. Despite the widespread endorsement of the programs and a large literature base,<sup>11-19</sup> there are few randomised controlled trials (RCTs) that clearly demonstrate their effectiveness in terms of health gains. This, in part, reflects the difficulty of conducting community-based intervention research in a setting where there is a high demand/high endorsement of the service, and use of lay course leaders over which there is little or no quality control. It may also reflect the limitations of the instruments used to detect improvements in health. Many studies of these programs are longitudinal and compare baseline scores on several tests with those administered months or years later. For example, Lorig et al. have reported statistically significant change in health behaviour and health status, four months to two years following participation.<sup>18,20,21</sup> The RCTs have yielded inconsistent results. While health behaviours change, improvements in health outcomes are only modest. A notable early study by Lorig et al. demonstrated a four-month decrease in pain in the treatment group compared with a wait-list group. There were no differences in disability as measured by the Health Assessment Questionnaire.<sup>22</sup> A UK-based study showed small decreases in

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fatigue, anxiety and depression.<sup>12</sup> A small Australian RCT<sup>15</sup> and a US GP-based RCT<sup>19</sup> found no changes in health status or pain. Finally, several studies have demonstrated reduced health care utilisation.<sup>13,18</sup> While this may not be a very good proxy for health status (as people learn to deal with their disease with less assistance from their doctor) it does represent a reduced financial burden on the population.

### Physical Therapy and Exercise

A systematic review of the effectiveness of exercise therapy in patients with OA of the hip or knee was recently undertaken by van Baar et al.<sup>23</sup> While eleven studies were identified for review, only six satisfied 50% of their validity criteria. Small to moderate beneficial effect of exercise therapy on pain, a small beneficial effect on disability and moderate to great beneficial effect based on patient global assessment were noted. Exercise therapy, including physiotherapy, are currently receiving considerable systematic evaluation and are likely to be applied more frequently, not only as a treatment option for OA, but as a pre- and post-orthopaedic surgery adjunct. The combination of physical therapy, joint protection advice and psychosocial support in formal rehabilitation programs may improve outcomes above any single intervention.

Other physical therapies such as therapeutic ultrasound (low level laser therapy) have only been examined in a few studies of modest quality. A recent Cochrane review indicated that ultrasound therapy appears to have no benefit over placebo or short wave diathermy for patients with OA of the knee.<sup>24</sup>

### Weight Loss

There is considerable evidence that obesity is associated with an increased incidence of OA, but there is little evidence to support the contention that reducing weight in those with established OA will improve symptoms. A small study by Toda et al. demonstrated a correlation between reduction in body fat (but not body weight) and reduced knee pain.<sup>25</sup>

### Joint Protection

Malalignment of the knee has been implicated in the progression of knee OA. In an 18-month follow-up study, varus or valgus malalignment were associated with a four to fivefold increase in medial or lateral progression and joint space narrowing.<sup>26</sup> In addition, recent studies suggest that bracing of OA knees through patella taping can reduce the symptoms and progression associated with advanced or severe knee OA.<sup>27-29</sup> Ambulatory aids such as heel and sole wedges are also an interesting option. While there have not been any RCTs reported, longitudinal studies of heel wedges suggest that they may reduce pain, especially for people with early or milder medial OA of the knee.<sup>30,31</sup> While there have been only a small number of studies on joint protection strategies, these interventions represent an emerging low cost range of treatment that could be considered.

## PHARMACOLOGICAL THERAPIES

### Paracetamol

Paracetamol is recommended as the first-line drug treatment for OA patients in a number of international guidelines.<sup>10,32,33</sup> This recommendation is supported by the results of some RCTs.<sup>34,35</sup> Paracetamol is effective in

reducing pain from OA and has a superior safety profile to non-steroidal anti-inflammatory drugs (NSAIDs) when taken regularly.<sup>36</sup> Despite the apparent equivalence of paracetamol and NSAIDs in RCTs, a recent study surveyed the treatment preferences of 668 people with OA and found that 50% of people found paracetamol less or much less satisfactory than NSAIDs, compared with 32% who found it about the same and 16% who found paracetamol either more or much more satisfactory than NSAIDs.<sup>37</sup> More recently, a study of patients with OA compared two cyclo-oxygenase-2 specific inhibitors (CSIs), celecoxib and rofecoxib, with paracetamol, and found that CSIs were more effective than paracetamol in reducing pain from OA in a short-term follow-up of six weeks.<sup>38</sup>

The role of paracetamol in mild to moderate OA has been promulgated because of its safety, particularly when compared with NSAIDs. Paracetamol is not, however, entirely safe, with daily doses above 4g associated with an increased risk of hepatic toxicity. The risk of hepatic toxicity is also increased in patients with established liver disease or who abuse alcohol.<sup>39</sup> In addition, paracetamol may interact with warfarin, causing an increased INR (International Normalised Ratio) response, particularly when maximal doses are employed.<sup>40</sup>

### Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

If paracetamol and non-pharmacological therapies are insufficient to control the symptoms of OA, then consideration must be given to prescribing NSAIDs. Prior to making this decision it would be ideal to assess the patient's gastrointestinal and renal risk factors (Tables 1 and 2).<sup>41,42</sup> In patients with gastrointestinal risk factors, the prescription of a CSI should be considered, particularly in those with multiple risk factors. In patients with renal risk factors, other treatment options should be considered before prescribing a NSAID or a CSI. If CSIs or NSAIDs are prescribed in patients with renal risk factors, the patient's clinical state should be monitored, in particular blood pressure and renal function.

**Table 1. Risk factors for upper gastrointestinal complications when taking NSAIDs<sup>41</sup>**

Age >65 years
Previous history of peptic ulcer disease
Previous history of upper gastrointestinal bleeding
Co-morbid medical problems
Use of oral glucocorticoids
Use of anticoagulants
NSAID = non-steroidal anti-inflammatory drug

**Table 2. Risk factors for renal complications when taking NSAIDs<sup>42</sup>**

Raised serum creatinine
Age >65 years
Hypertension
Congestive heart failure
Use of angiotensin-converting enzyme inhibitors
Use of diuretics
NSAID = non-steroidal anti-inflammatory drug

In patients with no gastrointestinal risk factors, it is appropriate to use NSAIDs, commencing at a low dose and titrating against efficacy. All currently available NSAIDs have been tested in randomised, placebo-controlled trials in patients with OA and rheumatoid arthritis. In these studies NSAIDs have been shown to be superior to placebo, but there has been no clear evidence suggesting one agent is more efficacious than another. The risk of upper gastrointestinal perforation, ulceration and bleeding associated with different NSAIDs has been investigated in several studies, which have demonstrated that certain NSAIDs are associated with an increased risk, up to four to five times that of other NSAIDs.<sup>43-45</sup> A recent Danish population-based study found that the frequency of upper gastrointestinal bleeding in people who use NSAIDs was 3.6 times higher than the remainder of the population not taking NSAIDs. For ibuprofen and naproxen, there was a clear trend of increasing risk by increasing dose, although the lowest doses were also associated with increased upper gastrointestinal bleeding. Overall, ketoprofen was found to be associated with the highest risk of upper gastrointestinal bleeding, followed by naproxen, indomethacin, diclofenac, piroxicam and ibuprofen.<sup>46</sup>

In those with gastrointestinal risk factors, conventional NSAIDs could be prescribed with an agent to reduce the risk of gastrointestinal bleeding. The co-prescription of misoprostol or omeprazole have both been shown to reduce the risk of ulcer complications in patients taking NSAIDs, although misoprostol is often poorly tolerated in older people and is now rarely used.<sup>47,48</sup> Conventional doses of histamine-2 receptor antagonists have not been found to protect patients from gastrointestinal events.

### **Cyclo-Oxygenase-2 Specific Inhibitors**

Cyclo-oxygenase is an enzyme that converts arachidonic acid to prostaglandin precursors, and has two forms—cyclo-oxygenase-1 and 2 (COX-1 and COX-2). COX-1 is a continuously expressed 'house keeping' enzyme found at sites where prostaglandins have a role, such as protection of the stomach and kidney, and activation of platelets. COX-2 is an inducible form of the enzyme and expressed at sites of inflammation and tissue damage. CSIs were therefore predicted to have less toxicity but equal potency compared with conventional NSAIDs. Four CSIs are currently (or soon to be) available in Australia—celecoxib, rofecoxib, valdecoxib and etoricoxib. Meloxicam, although not a 'coxib', is considered COX-2-selective, especially in low doses. The quality of evidence supporting the contention that meloxicam has lower gastrointestinal risk than NSAIDs is not as strong as for celecoxib and rofecoxib.<sup>49</sup> Multiple short- and long-term studies have demonstrated that the efficacy of CSIs in OA is equivalent to NSAIDs and superior to placebo.<sup>50</sup> The issue of whether CSIs are associated with reduced toxicity has been addressed in two large studies. The first of these was the CLASS trial (Celecoxib Long-Term Arthritis Safety Study) which compared celecoxib with diclofenac and ibuprofen in people with OA and rheumatoid arthritis. This study was first reported in 2000 by Silverstein et al.<sup>51</sup> with extensive re-evaluation and commentary by the US Food and Drug Administration (FDA) and comment by others.<sup>52</sup> The second study is the VIGOR trial, which compared rofecoxib with naproxen in people

with rheumatoid arthritis.<sup>53</sup>

In the CLASS study, based on the six-month data, celecoxib was reported to have reduced absolute risk for serious gastrointestinal complications when compared with NSAIDs, by about seven cases per 1000 treatment years. Subsequent analysis of the twelve-month data demonstrated a halving of this benefit. According to the FDA, the difference was not significant at either six or twelve months based on the protocol-defined primary safety endpoints. The FDA analysis of data from the VIGOR trial (comparing rofecoxib with naproxen) found a halving of serious gastrointestinal complications with rofecoxib, but no overall safety benefit due to a doubling of the relative risk for cardiovascular thrombosis among those receiving rofecoxib. While no such increase in cardiac events was found in the CLASS (celecoxib) study, prophylactic aspirin was not an exclusion criterion in this trial, but was the major exclusion criterion in the rofecoxib study.<sup>53</sup> It is unclear whether the observed increase in cardiovascular thrombotic events is specific to rofecoxib, or if naproxen (the comparator NSAID in the VIGOR study) has a cardioprotective effect.<sup>54</sup>

A recent observational cohort study among about 150 000 elderly patients (>65 years) in Canada, compared the frequency of gastrointestinal haemorrhage in people prescribed a range of NSAIDs. When compared with 100 000 control patients not taking NSAIDs, the frequency of gastrointestinal haemorrhage was the same among people taking celecoxib (rate ratio 1.0, 95% CI 0.7 to 1.6) and more frequent in people taking rofecoxib (rate ratio 1.9, 95% CI 1.3 to 2.8), and diclofenac plus misoprostol (rate ratio 3.0, 95% CI 1.7 to 5.6), with the highest frequency in people taking NSAIDs (rate ratio 4.0, 95% CI 2.3 to 6.9).<sup>55</sup>

Benefits of CSIs include lack of anti-platelet effect (allowing the drugs to be used peri-operatively) and reduced liver toxicity.<sup>50</sup> There is no evidence, however, that CSIs are less likely than NSAIDs to increase blood pressure, negate the effects of antihypertensive drugs, worsen heart failure or renal function, or cause swollen ankles.<sup>56</sup> Therefore, both NSAIDs and CSIs should be used with caution in those with renal risk factors.

### **Other Analgesics**

Products containing codeine (30 mg) and paracetamol (500 mg) have been demonstrated to provide greater pain relief than paracetamol alone in the treatment of patients with OA of the hip.<sup>57</sup> However opioid side effects, such as nausea, may limit the escalation of such therapy. Dextropropoxyphene, with or without paracetamol, is only modestly effective.<sup>58</sup> Tramadol, a centrally acting synthetic opioid, which also inhibits the reuptake of noradrenaline and serotonin, is also useful in those with unresponsive moderate to severe OA.<sup>59,60</sup> Tramadol is better tolerated and less likely to be addictive than other opioid analgesics,<sup>61</sup> however it has a propensity for drug interactions, which is a significant problem in the elderly.

## **COMPLEMENTARY AND ALTERNATIVE MEDICINES**

### **Glucosamine and Chondroitin**

Glucosamine and chondroitin are components of the proteoglycan matrix structure of cartilage. Both these nutritional supplements have demonstrated efficacy in the management of OA in a number of clinical trials.<sup>62,63</sup> A large, randomised controlled study of glucosamine

sulphate in patients with OA of the knee confirmed the symptomatic benefit of glucosamine, and, in addition, suggested a possible disease-modifying role.<sup>64</sup> Both glucosamine and chondroitin have been available in Europe for many years as a treatment for OA, and have more recently become popular in Australia and the USA. A large National Institutes of Health funded study of glucosamine and chondroitin in OA patients is underway and will help confirm or refute these findings. Long-term studies<sup>64</sup> and a meta-analysis<sup>65</sup> suggest that glucosamine has an extremely benign side effect profile, comparable to placebo in clinical trials.

### **S-Adenosylmethionine (S-AMe)**

S-Adenosyl-L-Methionine (S-AMe) is a naturally occurring compound involved in several important biochemical pathways, including transmethylation and trans-sulphuration reactions. The administration of S-AMe to patients with OA seems to have a substantial therapeutic effect, although its mechanisms of action are largely unknown. Several clinical trials have been undertaken, mostly in Europe and North America (total enrolment about 22 000 patients).<sup>66-72</sup> Most of the studies were published in the late 1980s and subsequent reviews suggest that S-AMe is as effective as NSAIDs in reducing pain and improving functional limitation in patients with OA, without the adverse effects often associated with NSAID therapies.<sup>73</sup>

### **Avocado/Soybean Unsaponifiables (ASU)**

ASU, not yet available in Australia, is made of unsaponifiable extracts of one-third avocado oil and two-thirds soybean oil. *In vitro* studies have shown that ASU stimulates collagen synthesis in articular chondrocyte cultures and may promote transforming growth factor B-induced matrix repair mechanisms in articular cartilage.<sup>74</sup> Three randomised, placebo-controlled, double-blind clinical trials have been completed and support claims of efficacy and safety in the treatment of OA.<sup>75-77</sup> A recent review, pooling results from two of these trials, found beneficial effects from ASU on pain control, function and global arthritis assessment, compared with placebo, as well as a reduction in NSAID intake, without any serious adverse effects.<sup>78</sup>

## **INTRA-ARTICULAR THERAPIES**

### **Intra-Articular Injection of Corticosteroid**

In situations where OA is severe, painful, or inflamed, 'depot' preparations of corticosteroid may be injected into the joint to reduce discomfort and increase function.<sup>79</sup> Intra-articular injections of corticosteroids have been used in the treatment of knee OA for more than 30 years, but few studies have been undertaken to measure their effect.<sup>80</sup> Triamcinolone hexacetamide (not yet available in Australia) has been recommended in one study as the most efficacious preparation for intra-articular injection,<sup>81</sup> however little comparative data have been published, and other agents (e.g. methylprednisolone acetate) may be equally efficacious. Painful short-term OA 'flares' may benefit most from this type of treatment, as although effective, pain relief is usually short-term, lasting from one to four weeks. Joints should not generally be injected more than three to four times per year because of the risk of cartilage damage from repeated injections. Patients requiring more than this number of injections to control symptoms may be good candidates for surgery.<sup>33</sup>

### **Visco-Supplementation**

In joints affected by OA, the synovial fluid's capacity to lubricate and to absorb shock is reduced. These changes may partly be due to a reduction in the size and concentration of hyaluronic acid (hyaluronan) molecules naturally present in synovial fluid.<sup>82</sup> Injection of material designed to increase the viscosity and elasticity of the synovial fluid has been shown to be a beneficial therapy for OA,<sup>83</sup> and one recent study has indicated that hyaluronan may act to modify the structural organisation of the knee synovium in OA.<sup>84</sup> A number of different products are marketed for visco-supplementation in OA of the knee.<sup>85</sup> Hylan G-F 20 (Synvisc) is the only available agent in Australia, marketed for knee OA. It is provided as a course of three injections, given weekly, with a maximum recommended dose of six injections within a six-month period. The product has been registered in Australia as a device, implying that it only has mechanical effects as a joint lubricant and shock absorber. Injections can be given by any medical practitioner experienced in knee joint aspiration and injection techniques, using strict no-touch aseptic technique.<sup>78</sup> A recent review of 14 clinical trials of intra-articular hyalurons reported that they were, in general, more efficacious in reducing knee pain and improving function compared with placebo, and were comparable with conventional NSAIDs.<sup>86</sup> However, visco-supplementation is not effective in patients with severe OA.

Adverse events due to intra-articular hyalurons have been noted in a number of trials; however a 1996 review of clinical practice in Canada suggests that the incidence of adverse events is strongly influenced by injection technique. Seventy-nine per cent of adverse events were shown to resolve without sequelae.<sup>87</sup>

## **SURGICAL PROCEDURES**

A number of surgical options exist for patients with severe, refractory OA of the knee. These include arthroscopic debridement and lavage, ligamentous reconstruction, realignment osteotomy, unicompartmental and total knee arthroplasty, and arthrodesis. Evidence to support these interventions is weak, as there are very few published RCTs that compare surgical interventions either with each other, or with alternative non-surgical interventions in OA.

Arthroscopic surgery for OA of the knee can be used for either diagnostic purposes or surgical removal of damaged osteous or soft tissues (debridement). However a recent randomised, double-blind, placebo-controlled (sham surgery) study of arthroscopy<sup>88</sup> in OA of the knee revealed no benefit, which is consistent with earlier work.<sup>89-91</sup>

Total knee replacement and total hip replacement are the recommended treatment for severe knee or hip OA in most published consensus guidelines. Although most published studies are observational and focus on the survival of the prosthesis rather than the effectiveness of the treatment (e.g. Crawford et al., 1997<sup>92</sup>), joint replacement surgery offers substantial sustained relief for most people with end stage disease.<sup>93-95</sup>

## **OTHER TREATMENT OPTIONS**

A vast body of literature exists, involving small studies of variable quality, examining the efficacy and toxicity of other interventions in OA. Many of these studies

demonstrate promising results, and a range of compounds or procedures are being further evaluated in larger, higher quality trials. At this point, vitamin and mineral supplementation, ginger extracts, acupuncture, pulsed electromagnetic field therapy, laser therapy and many other treatments fall into this category and few recommendations can be made at this stage about their role in OA treatment.

## CONCLUSION

The treatment of OA in the elderly requires a thorough evaluation of all the patient's problems and needs, and implementation of appropriate non-pharmacological and pharmacological therapies. Non-pharmacological therapies should be enthusiastically applied, well before pharmacological treatment is considered. Paracetamol remains the drug treatment of choice in the majority of OA patients. When regular paracetamol (up to 4 g daily) is ineffective at controlling pain, NSAIDs are typically the next pharmacotherapy prescribed. In those with gastrointestinal risk factors, the CSIs, with their probable improved gastrointestinal safety profile, should be considered. Renal and cardiovascular side effects may occur with either the CSIs or NSAIDs and patients with renal risk factors should be monitored carefully, or different therapy considered. Patients who fail to respond to these measures may be considered for other therapy including intra-articular hyaluronan or corticosteroid, tramadol or opioids. Complementary and alternative therapies such as glucosamine, chondroitin, SAME and ASU, with their benign safety profiles, can be tried at any time, with some studies indicating that better results are achieved when these substances are taken early in the course of OA. When these measures fail to improve pain and function, a surgical approach will generally be necessary.

**Competing interests:** Dr McColl is a member of the Pharmacia/Pfizer Celebrex Advisory Board and has received payment for talks from Merck Sharpe and Dohme.

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Submitted: October 2002

Accepted after external peer review: November 2002