

Osteoarthritis

## Non-surgical treatment of osteoarthritis: a half century of “advances”

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Drugs should be used as *adjuncts* to non-pharmacological measures

In the 1950s and early 60s Sir John Charnley succeeded in developing components for total hip arthroplasty and demonstrated the remarkable success that could be achieved with this procedure in patients with osteoarthritis (OA). Charnley's adaptation of polymethylmethacrylate as a fixation interface between the metallic or plastic implant and the bone served as a major advance in the surgical treatment of severe OA.<sup>1,2</sup> Development of total knee arthroplasty followed. The materials and surgical techniques have improved steadily so that both of these procedures are associated with a high level of patient satisfaction. Most patients with OA of the hip or knee who undergo total joint arthroplasty experience clinically significant improvement in joint pain, function, and quality of life.<sup>3,4</sup>

Recommendation of total joint arthroplasty for the patient with OA, however, is tantamount to an acknowledgement of the failure of medical management. The surgical procedure is often performed after the patient has experienced years, or even decades, of pain and disability. Among all the pharmacological and non-pharmacological interventions promoted for treatment of OA in the half century since Charnley directed his attention to replacement of the arthritic hip, none approximates the effectiveness of arthroplasty.

The 1963 edition of the Cecil-Loeb textbook of medicine,<sup>5</sup> in discussing the treatment of OA, noted: “Analgesics, particularly salicylates, are useful in controlling the symptoms of osteoarthritis. Phenylbutazone is sometimes helpful when salicylates have failed, but the potential toxic reactions rarely justify its use in such a mild disorder. Systemic corticosteroid treatment is not recommended for osteoarthritis. Intra-articular injections of hydrocortisone acetate ... may be helpful for joints which fail to respond to simpler measures.”

Despite enormous increases in our understanding of pain mechanisms and of the metabolism, biochemistry, and molecular biology of articular cartilage since that time and our increasing recognition that OA is not merely a disease of cartilage but of all the tissues of the diarthrodial joint, our track record for the development of more efficacious drug treatment for OA is discouraging. In contrast with the striking progress that has been made during this period in the treatment of rheumatoid arthritis, no biological agents are available for treatment of OA in humans. On the other hand, by appropriate use of non-pharmacological measures supplemented by drug treatment, as discussed below, we can treat patients with OA more effectively than we have in the past.

Several examples substantiate this lack of progress in the pharmacological treatment of OA.

### NSAIDS

Over the past 30 years we have seen the marketing of a large number of non-steroidal anti-inflammatory drugs (NSAIDs). However, the magnitude of pain relief afforded by NSAIDs, and their superiority to placebo, is only modest. Improvement averages only about 20% relative to baseline, and differences between NSAID and placebo only about 15–20%.<sup>6,7</sup> For many patients, the magnitude of relief of OA pain with NSAIDs is no greater than that achieved with acetaminophen (paracetamol, APAP)—an over the counter analgesic approved for treatment of mild to moderate pain. As noted by Dieppe *et al*, the majority of large sized clinical trials comparing non-selective NSAIDs with APAP have shown only small effect sizes, with the distributions of the reduction in pain scores overlapping in more than 80% of all patients.<sup>8</sup> Nearly 50% of patients exposed to both APAP and an NSAID judged APAP to be about as good as, better than, or much better than their

NSAID, with the proportion of those preferring APAP increasing with age.<sup>9</sup> The results of n of 1 studies support these observations.<sup>10</sup> Similarly, in a recent double blind, crossover trial, some 45% of subjects preferred APAP even when an NSAID was significantly better than APAP in improving pain, function, and quality of life.<sup>11</sup> Thus, statistically significant differences between treatments do not necessarily translate into clinically significant differences.

“Patients often prefer to take paracetamol rather than an NSAID, even when the NSAID has more effect on pain”

The lack of satisfaction of patients and doctors with NSAID treatment is reflected by the results of an observational study by Scholes *et al*,<sup>12</sup> which indicated that fewer than 20% of patients with hip or knee OA in whom NSAID treatment was initiated were still taking the same drug 12 months later. The awareness of patients and health professionals of the serious, and potentially fatal, gastrointestinal and cardiovascular renal adverse effects associated with use of non-selective NSAIDs has generated increasing concern. Today, NSAID associated ulcers and ulcer complications are *the* major iatrogenic disease.

### COX-1 SPARING NSAIDS (COXIBS)

Coxibs were developed with the expectation that their COX-1 sparing effect would result in less gastrointestinal (GI) toxicity than non-selective COX-2 inhibitors. Since their approval by the Food and Drug Administration (FDA), the manufacturers have vigorously and successfully marketed celecoxib and rofecoxib to doctors and consumers. Among people over the age of 65 who are new to the NSAID market (that is, who have not taken a prescription NSAID over the past 12 months), about 50% of all NSAID prescriptions are now written for a coxib.

Have coxibs fulfilled their promise? Although rofecoxib decreased the incidence of serious NSAID associated GI events by 50–60%, relative to the non-selective NSAID, naproxen, in the VIGOR trial,<sup>13</sup> results of the large GI safety study of celecoxib, the CLASS trial,<sup>14</sup> are less clear,<sup>15</sup> and concomitant use of low dose aspirin for cardiovascular prophylaxis appeared to mitigate the gastroprotective effect of celecoxib.<sup>13</sup> Furthermore, retention of salt and water associated with inhibition of COX-2 may lead to oedema, congestive heart failure, hypertension, and reduction of the

effectiveness of antihypertensive drugs. Also, the adverse effects on bone associated with COX-2 inhibition<sup>16</sup> may be no less a problem with coxibs than with non-selective NSAIDs.

Is the enormous popularity of coxibs warranted? The incidence of symptomatic ulcers and potentially fatal ulcer complications (haemorrhage, obstruction, perforation) among subjects taking non-selective COX inhibitors is about 2–5% a year<sup>17, 18</sup>—that is, some 95% of patients who take non-selective NSAIDs do so *without* incurring a serious GI event. Furthermore, not all patients using non-selective NSAIDs are at identical risk for a GI catastrophe; a number of risk factors have been identified (for example, age, comorbidity, history of peptic ulcer disease, history of upper GI bleeding, anticoagulant treatment). A recent cost effectiveness analysis<sup>19</sup> led to the conclusion that coxibs are not cost effective among subjects who are not at high risk.

“Coxibs are no more effective in OA than non-selective NSAIDs but some may provide more protection against GI effects”

Despite claims that coxibs are a “super aspirin”,<sup>20, 21</sup> their efficacy in treatment of OA symptoms is no greater than that of non-selective NSAIDs.<sup>22–26</sup> As noted above, this leaves much to be desired. Indeed, in the VACT study, celecoxib, 200 mg/day (a dose recommended for treatment of OA), was not significantly more efficacious than APAP.<sup>27</sup> Although rofecoxib, 25 mg/day, was better than APAP in that trial, that dose is associated with a significantly greater incidence of side effects than 12.5 mg/day, which is the dose that is recommended for initiation of OA treatment and which, for many patients with OA, is as effective as the higher dose.

Furthermore, the incidence of myocardial infarction (MI) in the VIGOR study was, unexpectedly, fourfold greater among patients treated with rofecoxib than with naproxen. Although the absolute number of MIs was small; the study was not powered to compare the effects of the two treatments on MI; the comparability of the prevalence of risk factors for MI (for example, obesity, hypercholesterolaemia, diabetes mellitus, smoking) in the treatment groups was unknown; the dose of rofecoxib was 2–4 times greater than that used for treatment of OA; and the trial was conducted in patients with rheumatoid arthritis, in which the incidence of MI is about twice as great as that in OA, the FDA has required that the rofecoxib label contains a caveat

about use of this drug in patients predisposed to ischaemic heart disease.

In summary, coxibs have no greater efficacy than non-selective NSAIDs for treatment of OA. However, they may offer an important GI safety advantage for some patients with OA who are at increased risk for serious upper GI adverse events if they use a non-selective NSAID, although this benefit may be lost if the patient is an aspirin user. Furthermore, the adverse cardiovascular renal effects and adverse effects on fracture healing of coxibs do not differ significantly from those of non-selective NSAIDs, and selective COX-2 inhibition may be associated with an increased risk of vascular thrombosis. Thus, while coxibs may allow us to treat *some* patients with OA more safely than with non-selective NSAIDs, they carry considerable baggage and their use has created new concerns.

### TRAMADOL

Tramadol hydrochloride is a centrally acting analgesic that has  $\mu$ -opioid agonist activity and inhibits reuptake of norepinephrine and serotonin. The opioid and non-opioid activities are synergistic. Tramadol may be useful in management of moderate to moderately severe OA pain. The analgesic effect of tramadol is comparable to that of the NSAID, ibuprofen,<sup>28</sup> but because tramadol does not inhibit prostaglandin synthesis it has no adverse effects on the kidney, platelets, or gastric mucosa. It is said that the chief advantage of tramadol lies in the fact that tolerance and dependence are very uncommon with long term administration and this drug has, therefore, not been scheduled as a controlled substance. However, although health professionals and patients often have concerns about tolerance to opioids and physical and psychological dependence, Shuckit found that people age 60 or older account for fewer than 1% of patients attending methadone maintenance programmes,<sup>29</sup> suggesting that the prevalence of narcotic abuse among older people is low. Notably, the analgesia that can be achieved with tramadol is no greater than that with APAP/codeine and its side effect profile no more favourable,<sup>30</sup> although tramadol is considerably more expensive than APAP/codeine. A tramadol/APAP formulation has recently become available whose efficacy was comparable to that of APAP/codeine in a comparative clinical trial in patients with chronic low back pain and OA of hip or knee, with the incidence of constipation only about half as great as with the latter (11%, 21%, respectively).<sup>31</sup>

### INTRA-ARTICULAR HYALURONAN (IA HA)

IA injections of HA have been employed with some enthusiasm in the past few years for treatment of OA pain that has not responded to a programme of APAP and non-pharmacological measures.<sup>32</sup> Although the manufacturers have suggested that “viscosupplementation” is the basis for clinical improvement that, in some patients, may last for several months after such treatment, IA HA treatment increases the viscosity of synovial fluid only transiently.<sup>33</sup> In an analysis of 11 clinical trials of IA HA treatment, Dieppe *et al* found a pooled effect size of  $-0.48$ , with a 95% confidence interval (CI) of  $-0.72$  to  $-0.23$ .<sup>8</sup> In general, these studies have shown that IA HA treatment has only mild to moderate benefit. The effect size appears to be larger with chemically crosslinked preparations of HA, but this difference can be accounted for largely by a single outlier.<sup>34</sup>

“Intra-articular hyaluronic injections are expensive and only moderately beneficial”

Although IA HA treatment is expensive (approximately \$500 for a series of injections, in addition to the doctor’s fees for the 3–5 weekly visits required), it has been argued that it is cost effective, insofar as it is not associated with systemic effects and permits reduction in the patient’s NSAID dose, thereby reducing the risk of NSAID associated GI ulcers and ulcer complications and the cost of periodic laboratory studies needed to monitor chronic NSAID treatment. However, there is no evidence that reduction in NSAID dose or withdrawal of NSAIDs occurs with any frequency in patients treated with IA HA, and recent studies have failed to show that HA treatment is better than IA injections of saline or enzymatically degraded HA (in which the viscoelasticity has been drastically reduced).<sup>35–37</sup>

### GLUCOSAMINE, CHONDROITIN SULPHATE

Glucosamine and chondroitin sulphate have recently enjoyed striking popularity for treatment of OA.<sup>38</sup> They are sold widely in pharmacies, supermarkets, and health food stores, although not approved for use in OA by the FDA. Several studies have shown that the efficacy of glucosamine is greater than that of placebo and comparable to that of NSAIDs in patients with knee OA, with a better safety profile than NSAIDs.<sup>39</sup> However, the efficacy of neither glucosamine nor chondroitin sulphate has been examined in large

well designed placebo controlled trials. In a meta-analysis of six randomised, double blind, placebo controlled studies of glucosamine and nine of chondroitin sulphate, McAlindon *et al* concluded that moderate symptomatic benefit was demonstrated for both these agents, relative to placebo.<sup>40</sup> In studies of chondroitin sulphate, symptomatic improvement was apparent as long as 12 months after the onset of treatment. However, when only high quality or large size trials were considered, the effect sizes for glucosamine and chondroitin sulphate were diminished—that is, the better the study design, the smaller the therapeutic benefit. The pooled effect size in six randomised controlled trials of glucosamine, in each of which at least 100 subjects were enrolled, was found to be 0.18 standard deviation units, a result that would correspond with an average decrease in pain of only 4 mm on a 100 mm visual analogue scale (VAS).<sup>8</sup> Improvement of this magnitude, although it was statistically significant, would not be clinically significant.

A similar analysis of eight randomised clinical trials of chondroitin showed a pooled effect size of 0.78—that is, much greater than that for glucosamine. This corresponded with a difference in pain reduction between chondroitin and placebo of about 20 mm on a 100 mm VAS, although results of individual studies varied markedly.

Because company sponsorship has been shown to affect the likelihood of positive results,<sup>41</sup> it is notable that most of the published clinical trials of glucosamine have been supported by the manufacturer. Among 12 trials in which the manufacturer was clearly involved, positive results were obtained in all.<sup>42</sup> (In nine others that reported positive findings, the funding source was not identified.) In contrast, in three recent randomised, double blind trials in which the manufacturer did not have access to the raw data and was not involved in data analysis, glucosamine was no more effective than placebo.<sup>43–45</sup>

Is glucosamine “chondroprotective”? Results of two recent virtually identical randomised clinical trials,<sup>46–47</sup> both of which were supported by the manufacturer, have led to the suggestion that glucosamine not only improves joint pain in patients with knee OA but protects against articular cartilage damage, based upon analyses of changes in joint space width in the standing anteroposterior (AP) knee radiograph. However, concern has been expressed about the interpretation of the results of these studies because of limitations of the radiographic methods employed.<sup>48</sup>

An NIH supported multicentre study, the **Glucosamine Chondroitin Arthritis Intervention Trial (GAIT)**, currently in progress, is comparing glucosamine, chondroitin sulphate, the combination, and celecoxib to placebo in patients with knee OA. Although the primary outcome measure will be joint pain after 6 months of treatment, approximately 50% of the subjects will be maintained on treatment for 2 years and radiographs obtained at baseline will be compared with those obtained after 1 and 2 years of treatment. As an alternative to the standing AP radiograph, a metatarsophalangeal (MTP) view of the knee, which has been shown to possess excellent reproducibility in repeated examinations performed on the same day,<sup>49</sup> is being used in this trial. A recent single centre study, however, has suggested that the reproducibility of radio-anatomical positioning in paired MTP radiographs of OA knees obtained at a 14 month interval was appreciably lower than that of same day examinations.<sup>50</sup>

#### **TIDAL IRRIGATION (TI) OF THE KNEE**

Non-arthroscopic TI of the knee through a large bore needle has enjoyed some popularity in treatment of OA. Guidelines for the management of OA of the knee published in 1995 by the American College of Rheumatology (ACR) stated: “Most subjects who require more than 3–4 intra-articular injections of steroid per year to control symptoms are probably candidates for joint lavage or surgical intervention”.<sup>51</sup> An update of those guidelines published in 2000, however, was more circumspect and recognised the large placebo response that may accompany TI and that results of properly controlled studies of this procedure were not available.<sup>52</sup> Subsequently, the results of a randomised controlled trial of TI in 180 patients with knee OA, half of whom underwent a sham-irrigation procedure, have been published. The findings led the authors to conclude that “most, if not all, of the effect of TI” can be attributed to the placebo response.<sup>52</sup>

#### **ARTHROSCOPIC DÉBRIDEMENT AND LAVAGE**

In contrast with the often striking benefits associated with total joint arthroplasty (see above), another orthopaedic procedure employed widely for treatment of OA—arthroscopic débridement—has been shown recently to be no more effective than sham débridement. Moseley *et al* studied 180 patients with knee OA who were randomly assigned to receive arthroscopic débridement, arthroscopic lavage, or placebo

surgery (skin incision and simulated débridement without insertion of the arthroscope).<sup>53</sup> Patients and evaluators were unaware of the treatment group assignment. Outcomes, assessed over a 24 month period, included self reported pain and function and an objective test of walking and stair climbing. At none of the time points evaluated did either intervention group report less pain or better function than the placebo group and no clinically meaningful differences were noted between the three interventions. Insofar as these procedures are no more efficacious than placebo surgery, the authors concluded that the approximately \$3 billion spent on them annually in America might be used more effectively if directed elsewhere.

#### **DISEASE MODIFYING OA DRUGS (DMOADS)**

Our understanding of the pathogenetic mechanisms underlying breakdown of the articular cartilage and, to a lesser extent, the changes in subchondral bone in the OA joint, has increased enormously in the past decade. Unfortunately, this knowledge has not translated into better outcomes for the patient. It has, however, led to a major interest among drug companies and regulatory agencies in the development of DMOADs, agents whose main mechanism of action is directed not at relief of joint pain but at slowing the progression of radiographic changes of OA. Although a number of drugs and biological agents inhibit cartilage breakdown or stimulate antimetabolic activity of chondrocytes *in vitro*, and a few have been shown in animal models to prevent development of OA or slow the progression of disease in joints in which OA is already present, no treatment has yet been clearly shown to have structure modifying DMOAD activity in humans. It remains to be shown, furthermore, that DMOAD treatment will result in significant *clinical* benefit, such as a decrease in joint pain, improvement in mobility, reduction in the incidence of joint replacement surgery or in the number of applications for social security disability payments.

As noted above, claims that glucosamine exhibits DMOAD activity in humans have been viewed with some reservation because of concern about the interpretation of the radiographic changes on which the conclusion about DMOAD efficacy was based. Although it is generally considered that joint space narrowing is the best indicator of the progression of structural damage in OA, there is considerable debate about whether *any* of the radiographic techniques espoused for studies of OA progression are satisfactory for use in a

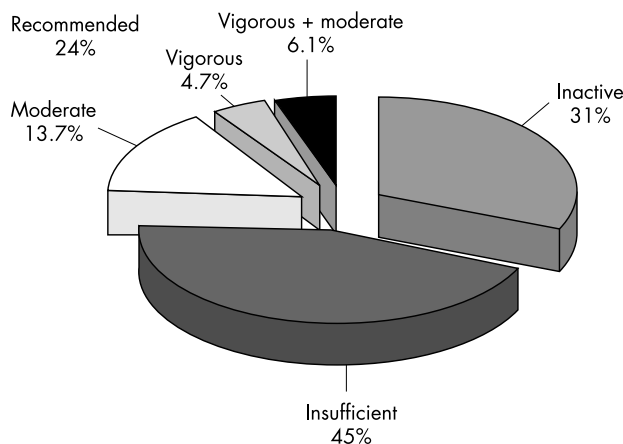
randomised placebo controlled trial involving a reasonable number of subjects and a reasonable duration of treatment.<sup>54</sup> Considerable interest exists also in magnetic resonance imaging, ultrasonography, chondroscopy, and measurement of biochemical or immunohistochemical “markers” of cartilage damage or repair, but none of these has been validated as an outcome measure for clinical trials of DMOADs.

As shown above, the new “advances” that have been promoted for treatment of OA over the past half century—non-selective NSAIDs, coxibs, HA injection, glucosamine, tidal irrigation, and arthroscopic debridement and lavage—are no more effective, or only modestly more effective, than placebo in treating the symptoms of OA, and tramadol appears to offer little advantage over the less expensive APAP/codeine. Efforts in the pharmaceutical industry to develop better symptomatic treatment for OA have been deflected or diluted by decisions to “chase the holy grail,” that is, to pursue development of a DMOAD. As noted, this has been done with no evidence that a DMOAD will be of symptomatic benefit and despite the fact that satisfactory outcome measures by which to evaluate the effect of a DMOAD on progression of structural damage do not exist.

### NON-PHARMACOLOGICAL MEASURES

None the less, we *can* offer the patient with OA better treatment today than heretofore. This can be achieved through use of *non-pharmacological* measures (for example, instruction in principles of joint protection, weight loss, exercise to improve fitness and strengthen periarticular muscles, orthotics, thermal modalities) that are now recognised as the keystone of OA treatment.<sup>32</sup> For example, several high quality randomised controlled trials have shown that aerobic exercise and strengthening exercise can help to relieve the symptoms of knee OA, with small to moderate effect sizes.<sup>8</sup> van Baar *et al* has suggested that compliance with an exercise regimen may be improved by maintaining contact with the patient and providing encouragement and motivation to continue treatment.<sup>55</sup> Group sessions are as effective as individualised exercise<sup>56</sup> and can greatly improve the cost effectiveness of the exercise intervention. Furthermore, the socialisation provided by group sessions may make the treatment more attractive over the long term than individual programmes.

Why is exercise important for the patient with OA? People with OA are much less active than those who do not have arthritis.<sup>57</sup> Only 24% of people with



**Figure 1** Levels of physical activity reported by people with arthritis. Only 24% of people with arthritis report and achieve levels of physical activity that are recommended for health. The remainder are essentially inactive or insufficiently active. (Prevalence and impact of arthritis among women—United States 1989–1991. *MMWR Morb Mortal Wkly Rep* 1995;44:329–34. Copyright © 1995 Wiley-Liss Inc. Reprinted by permission of Wiley-Liss, Inc, a subsidiary of John Wiley & Sons, Inc.)

arthritis report a level of physical activity sufficient to achieve health; 76% are doing nothing or are not sufficiently active (fig 1). Indeed, arthritis is the major reason that elderly subjects are not active or limit their activity.<sup>58–59</sup> It is a greater factor in limiting activity than heart disease, hypertension, blindness, or diabetes.<sup>59</sup>

Studies of cardiovascular health have shown that the aerobic capacity (cardiovascular fitness) of men with severe knee OA is more than 30% lower than that of men of comparable age who do not have OA.<sup>38</sup> Among subjects who were characterised as high risk, moderate risk, or low risk on the basis of their body weight, smoking history, and participation in exercise, those in the high risk group became disabled (that is, reported difficulty with performance of activities of daily living) some 7 years earlier than those in the low risk group.<sup>60</sup>

Disability in patients with OA may have more to do with their ability to remain active and physically fit and to maintain their body weight than with pathological changes in the OA joint. Subjects with knee OA expend more energy to walk—even at a slow speed—than age and sex matched controls without knee OA. People with knee OA work against much more than the OA present in the knee; the mechanics not only of the knee but also of the ankle, foot, hip, and low back are affected.

Even if we cannot cure OA, we can cure inactivity. In a longitudinal study of men who were assessed at 5 year intervals, Blair *et al* found that those in their 40s who were not performing sufficient physical activity and had low scores on a treadmill test had remarkably higher death rates than those who

were fit.<sup>61</sup> However, among those who were not fit at the outset but who *became fit*, the risk of mortality decreased by 44%. Each one minute increase in time on the treadmill at maximal effort was accompanied by a decrease of about 8% in mortality risk.

“With a comprehensive management programme many patients with OA can get better”

Patient education programmes offer benefits beyond those that can be achieved pharmacologically in symptomatic treatment of OA. A meta-analysis<sup>62</sup> showed that patient education interventions produced a benefit 20–30% as large as that achieved with NSAID treatment alone. Furthermore, the effects of the two are additive. Minor has emphasised that relevant education for the patient with OA is not education about, for example, joint anatomy or the definition of an osteophyte, but education in self management that emphasises the central role of the patient in managing the disease; teaches the skills required to permit the patient to manage medically and emotionally and maintain her role in society; and enhances self efficacy for successful self management.<sup>63</sup> As pointed out by Barlow and Lorig, if acquisition of knowledge alone were sufficient, few patients would be overweight and most would exercise appropriately and adhere to recommendations for taking their drugs.<sup>64</sup> Good patient education combines the provision of knowledge with the development of skills in problem solving and with motivational activities.

Self efficacy is the psychological construct that denotes a person’s confidence

in being able to carry out specific activities.<sup>65</sup> Kovar *et al* found that participation of patients with knee OA in an intervention that was based upon improving self efficacy resulted in decreases in joint pain and in the level of intake of analgesic and NSAIDs.<sup>66</sup> Improvements achieved by fostering self efficacy may significantly strengthen the efficacy of other interventions used in treatment of patients with OA and may be as great as that obtained with analgesics/NSAIDs.<sup>65</sup>

These observations have led to the development of a variety of self management programmes for patients with OA, such as the Arthritis Self Management Program (ASMP).<sup>67</sup> It is now clear that participation in a structured community based education intervention can result in significant improvement: for example, a 6 week programme in which subjects participated for only 2 hours a week significantly decreased pain, disability, and depression. Patients who participate in such programmes report greater performance of self management behaviours—for example, taking their medication properly and communicating with their healthcare providers. In a randomised controlled trial, participation in an arthritis self management programme resulted in a 20% decrease in pain and 40% decrease in doctor visits when assessed at a 4 year follow up interval, even with no reinforcement of the intervention over that interval.

The above comments should not be construed as nihilism about pharmacotreatment for OA pain. Rather, they are made to emphasise that drugs should be employed as *adjuncts* to non-pharmacological measures, such as those listed above, the use of which should be individualised to the specific needs of the patient. Belief that a person with significant OA can be managed successfully only by the prescription of a drug is likely to lead to failure.

However, non-pharmacological measures are far too seldom employed in the treatment of OA.<sup>68</sup> The reasons they are not used more often may be the cost, pressures on the time available to the doctor to educate the patient in the benefits of such measures, lack of conviction that these measures may be helpful, or other factors. Insofar as the adverse effects associated with non-selective NSAIDs and coxibs are dose dependent, it is important to recognise that implementation of non-pharmacological measures, supplemented by use of APAP, may permit a reduction in NSAID dose—or even complete withdrawal of NSAID treatment—without an increase in OA pain or in the requirement for opioids.<sup>69–71</sup>

It is notable that an education intervention aimed at reducing NSAID use in elderly subjects was highly successful when directed at nursing home staff<sup>71</sup> but failed when aimed at practising doctors in the same community.<sup>72</sup> Presumably, nursing home staff had ample time to implement the programme with their patients, whereas community doctors seeing a patient with symptomatic knee OA often have only a limited amount of time to spend with that patient and must deal with management of comorbidities that are often more serious than the knee OA.

There is too little understanding that, with a comprehensive management programme, *many patients with OA can get better!*<sup>73</sup>

The widely held notion that, once symptoms appear, OA is inexorably and inevitably progressive is incorrect. In many patients, the disease stabilises; in some, regression of joint pain and even of radiographic changes may occur.<sup>74</sup> For example, in a study of patients with knee OA who underwent clinical and radiographic evaluations on two occasions separated by an 8 year interval, Massardo *et al* found that while 20% of subjects worsened and many incurred severe disability, 13% improved, and two had striking improvement in function.<sup>75</sup> Among 63 subjects in whom paired knee radiographs were obtained at a mean interval of 11 years, only 33% had radiographic progression<sup>75</sup>; pain scores also tended not to worsen. Thus, many subjects with knee OA do not deteriorate either radiographically or symptomatically over long periods of observation. It is important to identify those patients with OA who will undergo more rapid progression of their disease and to direct efforts at early intervention to that high risk group, in particular.

As indicated above, we surely need better and safer drugs to treat OA symptoms. Thus, we need to recognise that synovitis is not the only cause of joint pain in a patient with OA and consider the effects of therapeutic modification of, for example, periarticular muscle spasm or stagnation of blood flow through subchondral bone in the OA joint.<sup>76</sup> We also need to understand why safe, inexpensive, and effective non-pharmacological measures are often not included in the treatment programme and why, even when they are prescribed, are often not incorporated into the healthcare behaviours of the patient. In dealing with OA as a public health problem, the greatest hope may lie with the behaviourist, rather than with the molecular biologist, biochemist, or pharmacologist.

## ACKNOWLEDGEMENT

Supported in part by NIH grants AR20582, AR433489, and AR44370.

*Ann Rheum Dis* 2004;**63**:117–122.  
doi: 10.1136/ard.2002.004606

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