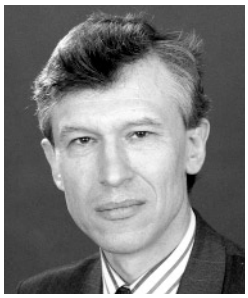
Editorial

Translating Research into Practice: Acetaminophen in Osteoarthritis Revisited



Whether clinicians should first use acetaminophen or a nonsteroidal antiinflammatory drug (NSAID) to treat osteoarthritis (OA) has preoccupied rheumatologists several years. A further contribution to this debate is published in this issue. Wegman and colleagues[1] report both a systematic review of some of the relevant randomized controlled trials and an overview of OA treatment guidelines. They conclude that, while NSAID are more effective, the first drug used to treat OA should be acetaminophen. They conclude that, while NSAID are more effective, the first drug used to treat OA should be acetaminophen. Although they favor acetaminophen because of the potential risks of NSAID treatment, they note that not all guidelines take the same approach.

As treating the pain of OA is such a common clinical problem, it seems an obvious area in which evidence-based treatment decisions should be used to build strong clinical guidelines. The question of whether to use acetaminophen or NSAID when treating OA is not novel, with trials dating from the 1980s. So why are we still debating such a basic question?

Providing an answer involves dealing with fundamental issues on the nature of clinical evidence, its translation into practice, and the role of clinical guidelines. Although such problems extend throughout medicine, exploring their impact on the narrow question of pain control in OA highlights the problems in developing evidence-based clinical care.

EQUATING EFFICACY AND TOXICITY

The overall assessment of Wegman and colleagues is supported by an earlier analysis from Courtney and Doherty[2], who evaluated a wider range of current evidence. They recommended nonpharmacological interventions should be the core element in managing OA, that acetaminophen should retain a pivotal role in drug treatment of symptomatic OA, and that NSAID should be considered as additional treatments whose use would be defined by individual patient factors.

One explanation for different groups of experts reaching dissimilar conclusions after evaluating virtually identical trial data is the way in which they restrict the use of information from non-trial sources such as longterm toxicity surveys. The analysis in the recent Cochrane review on acetaminophen[3], which evaluated 6 trials involving 1689 patients, concluded NSAID are superior to acetaminophen. However, it focused exclusively on risks and benefits shown in the trials themselves, and ignored information from other sources, which may be more important in defining longterm toxic effects of treatment.

There are clearly difficulties in balancing efficacy and toxicity. NSAID have significant toxicities, which can be quantified using standard methods[4]. There is also wide agreement on assessing efficacy in OA trials. However, there are no rules for balancing these 2 sides of the equation. Therefore some experts place more weight on toxicity and others on efficacy. The advent of the coxibs has reduced some, though not all, risks of serious adverse effects with NSAID, and this may swing the balance towards antiinflammatory drugs[5].

An associated problem is the continuing expansion of the clinical trial database. The conclusions in any metaanalysis must be tempered by the time it was undertaken, and new trials can modify the situation. Since Wegman and colleagues closed their metaanalysis in December 2001, 2 further randomized controlled trials have been published. Geba, *et al*[6] compared rofecoxib and celecoxib with acetaminophen in 382 OA patients over 6 weeks. More patients treated with acetaminophen discontinued early due to lack of efficacy. Initial and late efficacy, especially pain relief, was greater with coxibs. Case and his colleagues[7] compared diclofenac with acetaminophen in 82 OA patients over 12 weeks. There were early and sustained clinically and statistically significant improvements with diclofenac but not

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with acetaminophen. Thus the evidence of efficacy increasing favors NSAID. However, it remains likely that acetaminophen is still the safer treatment, leaving the problem of balancing risks and benefits essentially unchanged.

THE LIMITS OF TRIALS

OA trials, like many clinical trials, tend to exclude the elderly and patients with comorbid conditions like cardiac and renal disease, and enrol the relatively restricted healthy group of patients with OA who meet the American College of Rheumatology diagnostic criteria. Such strict exclusion and inclusion criteria raise substantial concerns about the generalizability of the findings, as OA patients who need treatment often have less clear-cut diagnostic features, are often very old, and frequently have multiple illnesses. As those patients who are excluded from trials are likely to be at greater risk of drug-induced toxicity, the design of trials pushes the balance away from lower risk treatments like acetaminophen, and this requires a balancing adjustment in an overview of the area.

The clinical trial evidence base has several other negative influences. These include poor trial quality, particularly with non-drug treatments[8], systematic bias from under-reporting of trials, especially if they are pharmaceutically funded[9], and the potential irrelevance of trial outcome measures like WOMAC (Western Ontario and McMaster Universities OA Index) to routine practice. Discrepancies between standard patient-based measurements and patients' narrative accounts suggest an over-reliance on doctor-based assessments can prejudice the appraisal of whether treatments are successful[10].

Trials, because of their focus on tightly-defined patient populations, often ignore ethnic and cultural diversity. Such diversity can not only affect biological outcomes like toxicity, but also influence healthcare beliefs and thus responses to treatment. It is important not to confuse efficacy, shown in carefully controlled trials, with overall clinical effectiveness. However, whether this means we should undertake large studies to determine clinical effectiveness remains questionable. Judging the role of a treatment can only be partly evidence-based, and there must be some room for interpretation of results in the light of experience.

PATIENTS' PREFERENCES

Patients have central roles in determining their own care and have variable preferences when choosing treatment, especially in areas such as risk. Patients with very defined or idiosyncratic views may be under-represented in studies, since they will not wish to be randomized to a treatment they have not chosen. This may vary across cultural and ethnic backgrounds, relating to beliefs about healthcare in general and treatment in particular. Relevant examples include preferences for non-drug therapy, complementary therapy, or traditional medicine, and invasive treatments such as injections.

Several studies have directly reported patients' preferences in this area, although their findings need to be interpreted with caution. In one large study Wolfe and colleagues[11] sent postal questionnaires to 1799 patients with OA, rheumatoid arthritis, and fibromyalgia. Overall, patients preferred NSAID, although this preference was less in the elderly and in those with OA. Wolfe and colleagues concluded that if safety and costs were ignored, there would rarely be a reason to recommend acetaminophen over NSAID, since only 14% preferred acetaminophen. However, when safety and costs were entered into the equation, they believed acetaminophen should be tried first, as 38% of patients found it was as effective or more effective than NSAID, and it remains safer and cheaper. Pincus, *et al*[12] reported the findings of a 15-minute telephone survey in 300 patients, including 172 with OA. Twenty-four percent of patients who took acetaminophen rated it "very helpful" compared to 31% for ibuprofen and 56% for diclofenac. However, drug continuation beyond 24 months was reported by 33% of patients with acetaminophen but only 19% for diclofenac. This was because acetaminophen was less often discontinued due to toxicity. This mirrors the findings of Wolfe and colleagues and shows the complexities of balancing short-term efficacy with longterm toxicity.

Treatment withdrawals are related to adherence to treatment interventions. Adherence is another barrier to treatment success. Estimates suggest that adherence to any intervention in OA is between 50% and 95%, but as these estimates are mainly derived from clinical trials, the real levels in clinical practice are likely to be much lower[13]. Few trials focus on adherence as a key outcome measure, although there is some evidence that in OA, patient adherence is increased with coxibs compared to conventional NSAID[14]. Linked to questions of adherence is the fact that acetaminophen is freely available "over the counter." Many patients will have already taken it prior to seeking medical advice, and may not view it in the same way as a medically prescribed NSAID. Further, the most effective dose of acetaminophen, 2 tablets 4 times daily, is more intrusive than single or twice daily doses of most NSAID, which will be likely to reduce adherence to its use in routine clinical practice.

CLINICIANS' VIEWS

There is evidence in rheumatoid arthritis[15] and OA[16] and across a spectrum of rheumatic disorders[17] that clinicians may have different views from their patients on the risks, benefits, and values of different treatment approaches. Despite such differences, patients' choices of treatment are strongly influenced by the health care professional caring for them. Despite, or perhaps because of, the profusion of information available, clinicians' views are only partially

evidence-based. Professional background has a major influence. Therefore physiotherapists will invariably focus more on exercise, while physicians will focus more on drug treatments. Local healthcare systems provide widely different treatment options; for example, hydrotherapy is used far less in the UK than in Central Europe. Whatever the evidence base, clinicians will not advocate treatments that conflict with their own beliefs. This problem is compounded where clinicians are not involved in clinical trials, either because of personal choice or working environment, as they will feel little ownership of any data generated.

GUIDELINES AND THEIR ALTERNATIVES

Theoretically, guidelines provide explicit recommendations and influence practice through a formal process of disseminating advice on effective management. Ideally, they should identify and eliminate ineffective or unnecessary treatment and deliver high quality care and reproducible standards[18]. It is unlikely they actually achieve any of these rather grandiose aims and aspirations. In a critique of OA guidelines, Dieppe pointed out their many limitations[19]. First, they use a constrained or even distorted evidence base. Second, they are aimed at the average patient, and not the individual patient. Finally, the opinions in most guidelines are derived from the views of small numbers of physicians, and often minimize the assessments of other stakeholders like therapists and patients. As no one is average, each individual patient with OA will have different needs and priorities, making the application of guidelines developed for the average patient often irrelevant in the individual case. He recommended moving from protocols to statements of principles and moving from guidelines to the provision of "toolboxes" or options for both patients and professionals.

It is over 10 years since we were first involved in producing OA guidelines[20]. The sentiments underlying these guidelines were revisited some years later[21] in an attempt to ensure patients received high quality care. There have been many guidelines produced in the ensuing years, and their benefits and drawbacks are regularly reexamined[22,23]. It is almost certainly too naïve to ask simply whether or not they are useful. In some circumstances guidelines can have a significant role in defining clinical practice, although this is usually focused around a single treatment option in a single regional or national setting. For example, within the UK, guidance from the National Institute of Clinical Excellence has had a significant effect on the use of coxibs[24]. General guidelines have less significant effects, but they set the tenor for the pattern of medical care.

In OA it seems eminently sensible for patients to try acetaminophen before they take an NSAID. However, most patients will already have tried this prior to seeking medical advice. Therefore a policy of clinicians always recommending acetaminophen seems bound to be impractical in routine practice. On the other hand, always giving NSAID appears equally futile. A balanced approach, treating pain with acetaminophen and NSAID singly or in combination, seems most appropriate, with the provisos that patients should not be exposed to NSAID for too long and that the elderly and unwell would be best advised to avoid them if possible.

DAVID L. SCOTT
King's College Hospital,
Department of Rheumatology,
Denmark Hill,
London SE5 9RS, UK;
GABRIELLE KINGSLEY,
Department of Rheumatology,
University Hospital Lewisham,
London, England.

Address reprint requests to Prof. D.L. Scott, Rheumatology Unit, Dulwich Hospital, East Dulwich Grove, London SE22 8PT, England. E-mail: david.l.scott@kcl.ac.uk

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