Do patients with osteoarthritis get the clinical research they need?

The most obvious and laudable reason for doing clinical research is, of course, to benefit the patients. Other motives that are sometimes important are to earn money, to increase chances of getting the next post, to become famous, or to satisfy curiosity. Such incentives are not necessarily bad. Indeed, the high level of competition in healthcare research may very well be more innovative and productive—and therefore more beneficial to the patients—than more centralised research approaches.

A particular piece of research may occasionally fulfil all five motives, but it would be the exception rather than the rule if research agendas overall matched even remotely what the patients need most. For example, according to the WHO, the combined investment in research and development into acute respiratory infections, diarrhoeal diseases, and tuberculosis—which kill over seven million people a year—amounts to 0.2% of global spending on health research and development, though these three diseases account for almost one fifth of the global disease burden.

Most new interventions, by far, are developed by industry and it is no wonder that industry chooses to go where the market is. For common diseases in the developed world this leads to the development of an array of drugs belonging to the same therapeutic class. Clinical testing of all those drugs consumes a considerable amount of financial and human resources, and clinicians sometimes complain that their colleagues have “occupied” the patients by trivial trials of “me too drugs” for years to come, making it impossible to start trials of greater relevance to the patients.

Is osteoarthritis an exception to this general state of affairs? In this issue of the Annals, Chard and colleagues review 50 years of research on interventions for osteoarthritis of the knee. They report that most of the research was on drugs (59%) or on surgery (26%). The remainder of the research concerned psychotherapy, alternative treatments, education, and behavioural change. The authors note that these less commonly researched areas have gained momentum in more recent times and they state that these shifts in the research agenda are in the same direction as calls for change by consumers. They conclude that the current research agenda appears to mirror consumers’ wishes.

Before accepting this interesting conclusion we need to ask two questions. Firstly, what are the consumers’ wishes? Secondly, and equally important, what type of research has actually been done? It might also be relevant to ask what was its quality? Did it in general lead to reliable conclusions?

Chard and colleagues do not say what the consumers’ wishes are but refer to an unpublished manuscript and to a report from the National Health Service. Whatever consumers’ wishes might be they are indisputably important, but they are not necessarily the best basis for research prioritisation, and they should certainly not be the only basis. For example, many consumers call for more research on alternative treatments, though the likelihood that such research will lead to important improvements is quite small. It might also be argued, for example, that it is important for patients to consider the use of resources in the National Health Service as patients fundamentally “compete” for a share of the limited resources made available to health care. When large resources are used on interventions which are suspected of being ineffective, there is an urgent need to summarise the treatment results in a systematic review, or, if no high quality randomised trial has ever been done, to ensure that one is performed.

As for the second question, it is useful that Chard and colleagues divide the research into six major areas, but this does not provide a sufficient level of detail for the type of conclusion they draw from their review. For example, the authors do not report the number of drug trials which involved non-steroidal, anti-inflammatory drugs (NSAIDs), though it must have been high. One of the authors previously identified 149 trials of NSAIDs in osteoarthritis and noted that no fewer than 147 of them had compared one NSAID with another. Only two trials compared an NSAID with an analgesic, and these trials were only published quite recently, in 1991 and 1993. It is noteworthy that in Australia in 1994, 36% of the people taking NSAIDs received them for osteoarthritis, 42% for sprain and strain or low back pain, and only 4% for rheumatoid arthritis. This corresponds poorly with the fact that NSAIDs do not seem to be better than simple analgesics for osteoarthritis, and that official guidelines recommend acetaminophen as the initial drug of choice. For sprain and strain, the situation is even worse: not a single high quality trial has compared an NSAID with acetaminophen, although—or because, depending on whose perspective one takes, that of the patient or that of industry—there is no reason to believe that NSAIDs would be any better. As these examples indicate, research agendas can have profound effects on subsequent practice.

There are no important differences, in effect, between different NSAIDs or different doses of the same drug. It is therefore reasonable to say that consumers deserve less “me too research”. They also deserve better research, particularly on surgical methods. Half of the papers included in the review were reports of randomised trials, but only 13 of the 239 (5%) papers on surgery described randomised trials. Although observational studies on long term outcome after surgery may be useful as a quality control, the effect and adverse effects of surgery need to be documented in randomised trials just as for any other type of intervention. There are special problems in designing and performing surgical trials, but they can be overcome, and if such trials are not done, the patients may fare badly. For example, a new cement for hip and knee replacements, Boneloc, turned out to lead to instability and many patients had to have a further operation. If the cement had been studied initially in a randomised trial, as described in the original development plan for the cement, this detrimental effect would have been detected much earlier, and the ensuing scandal might have been avoided.

I agree with Chard and colleagues that systematic reviews, including Cochrane reviews, should allow high quality observational data to be included. But it should be done with great caution and only in exceptional cases—for example, when adverse effects have been insufficiently described in randomised trials. When no randomised trials have been performed, it is usually better to report this deficiency rather than to include cohort studies, as they are too unreliable for estimation of any possible therapeutic effect. The Cochrane Non-randomised Studies Methods Group is currently working on guidelines on when and how, and with what precautions, such data might be included in Cochrane reviews. The possible bias that may be
introduced by relying on non-randomised comparisons of interventions can be large. For example, a meta-analysis of cohort studies of hormone replacement therapy showed protection against coronary heart disease, with a relative risk (RR) of 0.50 (95% confidence interval 0.43 to 0.56), which was not confirmed in a large randomised trial, RR=0.99 (0.80 to 1.22). Thus a 50% reduction in heart disease, with a narrow confidence interval, proved to be spurious and it is remarkable that there was not even an overlap between the two confidence intervals. The importance of randomisation as a principle and, indeed, of correct randomisation where it is impossible to foresee which treatment the next patient will receive, cannot be overstated. It has been shown that randomised trials with inadequate or undescribed allocation methods exaggerate the estimated effect by 33 to 41%, on average.

Chard and colleagues call for more research comparing different types of interventions, in various stages of the disease. This is important not only for osteoarthritis but for most other diseases. One way of promoting this might be to form transdisciplinary research teams, whose aims should be to identify gaps in knowledge and propose specific research projects. Cochrane reviews and the type of review reported by Chard and colleagues can be helpful in this respect.

Skewness in research priorities can be changed for the better—for example, by governmental initiatives providing funding for research that is unattractive to industry. By setting aside 1.5% of its annual budget for systematic reviews and clinical trials, the National Health Service in the UK has given its researchers a unique possibility, envied by most other countries, for increasing the share of research which is directly relevant for the patients. It is tempting to propose that the medical industry—which is generally much more wealthy than governments—should be taxed a certain percentage of its gross income for subsequent allocation to such research. After all, the industry could not exist without the willingness of the patients to contribute to clinical research and of society to provide the facilities for such research. In Denmark, for example, a modest 2% taxation of this income would, for drugs alone, amount to more than 200 million Kr annually. Such taxation would have a trivial impact on the industry, and if agreed at a supranational level, there would be even less incentive for the industry to move elsewhere. But it would mean that the necessary research could be done.

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