

In addition to providing selective evidence and biased presentations, Merck counseled its representatives to use an array of subliminal selling techniques to affect prescribing — potentially undermining the ability of physicians to choose drugs strictly on the basis of the risks, benefits, and costs for a particular patient. For example, in a training course on selling skills, Merck taught representatives to mimic the words and body language of doctors during sales calls. The curriculum explained that “mirroring is the matching of patterns, verbal and non-verbal, with the intention of helping you enter the customer’s world. It is positioning yourself to match the person talking. It subconsciously raises his/her level of trust by building a bridge of similarity.”<sup>5</sup>

The committee hearing raised serious questions about the marketing practices used by Merck, but it would be a mistake to restrict the lessons learned to a single company. The testimony we heard indicated that Merck’s marketing practices may be less aggressive and more ethical than those of many of its competitors. What is needed is a broad assessment of the ways in which all new drugs are promoted and prescribed in the United States.

As a policymaker, I see a need to enhance the FDA’s resources, authority, and oversight of new drugs. The agency does not review all industry promotional material (such as the Cardiovascular Card) quickly; it should have the resources to do so and the authority to require review before dissemination. The FDA should also have more authority to ensure that key information is promptly incorporated into drug labels, and warn doctors about potential safety risks. In the case of a drug such as

rofecoxib for which there are serious outstanding concerns about safety, the agency should have the authority to restrict advertising until these concerns have been adequately addressed by further research.

Legislative reform will not be successful, however, without attention to this issue in hospitals and doctors’ offices. All the Merck documents discussed above, and many others, are available on our committee’s Web site.<sup>5</sup> Practicing physicians, journal editors, and leaders of associations of medical professionals may find these documents useful as they develop new strategies to keep promotional efforts from distorting clinical care.

As we move forward, it is important to recognize that physicians, drug manufacturers, regulators, and policymakers all share the same goal: realizing the vast potential of safe and effective new drugs for improving the health of Americans. We all share responsibility for ensuring that important evidence translates into sound medical practice.

1. Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. *Lancet* 2005;365:475-81.
2. Dai C, Stafford RS, Alexander GC. National trends in cyclo-oxygenase-2 inhibitor use since market release: nonselective diffusion of a selectively cost-effective innovation. *Arch Intern Med* 2005;165:171-7.
3. Rose JL. Physicians’ expectations of industry and sales personnel. Chicago: American Medical Association, 2002.
4. FDA Advisory Committee briefing document NDA 21-042 s007 — Vioxx gastrointestinal safety. Rockville, Md.: Food and Drug Administration, 2001.
5. Committee on Government Reform, Minority Office, U.S. House of Representatives. Merck documents show aggressive marketing of Vioxx after studies indicated risk. (Accessed June 2, 2005, at <http://democrats.reform.house.gov/story.asp?ID=848>.)

## Tailoring Arthritis Therapy in the Wake of the NSAID Crisis

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In recent months, physicians and patients have been presented with a confusing array of decisions by the Food and Drug Administration (FDA) and the pharmaceutical industry regarding the use of non-steroidal antiinflammatory drugs (NSAIDs): Merck

withdrew its cyclooxygenase-2 (COX-2) inhibitor, rofecoxib, from the market; a closely divided FDA advisory panel recommended continuing the marketing of rofecoxib and other COX-2 inhibitors; and the FDA has requested that Pfizer suspend sales of valdecoxib in the U.S. market, contrary to the recommendation of its advisory committee (although Pfizer is planning discussions with the

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FDA to explore the possibility of resuming these sales). To complicate matters further, new concerns have arisen about the safety of naproxen, an NSAID that is not in the COX-2 class and that has been considered safe enough to be sold over the counter for years. The FDA will now require that black-box warnings about cardiovascular and gastrointestinal risks be included with all these agents.

Although the debate over the safety of these drugs continues, thousands of more circumscribed — and more urgent — debates take place every day in the offices of physicians throughout the country. We are confronted with more questions than we can answer on the basis of the available data, but our patients need advice now, and their concerns cannot be deferred while we wait for the results of more research. Each case must therefore be worked through individually in order to derive the best plan for the particular patient's circumstances. The problem is best framed with a few examples.

One patient in my own rheumatology practice, for example, was a retired professor of medicine who had a complex connective-tissue disorder. Although this disease was kept in relatively good control with low doses of corticosteroids, his joints periodically became inflamed and painful. It didn't happen every day, but it occurred with enough regularity to interfere with his tennis game, his favorite recreational activity. He had found through years of trying various arthritis medications that rofecoxib was the best medication for controlling the problem with his joints. Other conventional and COX-2-selective nonsteroidal drugs simply did not afford him the same degree of relief. Unfortunately, if he took a 25-mg dose of rofecoxib for more than a few days, painful ulcers developed in his mouth. This problem recurred each time he took the drug for several consecutive days, so he was confident that it was drug-related. With some trial and error, he found that one pill taken before he played tennis was sufficient to allow him to get through the day without difficulty and without the side effect of mouth ulceration.

This patient, of course, was better informed than most regarding the potential adverse effects of rofecoxib. But both he and I thought it unlikely that this type of rofecoxib use would have long-term cardiovascular consequences, and his quality of life was improved by the enjoyable physical activity the pain relief permitted him. It is also likely that the rest of his musculoskeletal system benefited substan-

tially from the exercise, so that in his case, the withdrawal of rofecoxib from the market has meant a significant diminution of overall health status.

A second patient whom I have cared for has rheumatoid arthritis that developed two decades ago, before highly active therapeutic agents became available. She has extensive and irreversible joint deformities, has undergone numerous joint operations, and has had recurrent infections. A bleeding ulcer, probably related to long-term use of NSAIDs, resulted in a six-month hospitalization, during which she underwent several surgical procedures and had postoperative wound infections and delayed healing. After being discharged, she strongly desired to return to the naproxen therapy that had worked for her in the past. But the medication that gave this patient the relief from her joint pain could not be prescribed because of the obvious safety risks. She was subsequently given a prescription for a COX-2 inhibitor, which caused no gastrointestinal problems but which she said was never quite as effective as naproxen at alleviating her joint pain.

More recently, I evaluated a woman who had discontinued celecoxib therapy — despite the fact that it had controlled her joint pain — because of the well-publicized questions regarding its safety. Her medical history included recurrent colon polyps, and she had a strong family history of colon cancer. The recent trial of celecoxib suggesting that it increases cardiovascular risk in fact also indicated that it may slow the growth of colon polyps, which would be expected to reduce the patient's risk of colon cancer. I advised her to return to celecoxib, which remains available for prescription use, since its efficacy and safety profile favored its use in a patient such as her.

As these instances demonstrate, there are enough factors to be weighed in the choice of an arthritis medication that the risks and benefits ought to be considered on a case-by-case basis by a physician who knows the patient. Until we have data from large-scale studies, which is unlikely to be soon, it makes sense to weigh the benefit achieved from treatment against the risks of adverse events that are likely to be encountered with traditional NSAIDs (i.e., gastrointestinal side effects) and coxibs (i.e., increased rates of cardiovascular events).

In most cases today, several of these medications are still tried before the most beneficial one is selected. Some patients in my practice claim that rofecoxib was the only drug that worked for their arthritis pain. Although the reasons for such selective re-

sponses remain obscure, it suggests that this drug had some characteristics that distinguished it sufficiently from others in its class that it had unique benefits in some patients. The field of pharmacogenomics is in its infancy, and it will probably be years before we fully understand the biologic basis of these differences. In the meantime, having an array of drugs to choose from, including multiple COX-2-selective agents, would enhance our ability to optimize therapy.

Patients with arthritis and their physicians have covered some of this ground before. A few years ago, questions were raised about the safety of drugs

used in the treatment of rheumatoid arthritis, including leflunomide and the tumor necrosis factor inhibitors. Ultimately, these drugs survived those challenges, and they remain mainstays of rheumatoid arthritis therapy. Indeed, it is the availability of these highly active agents that has freed some patients with rheumatoid arthritis from the need for any form of nonsteroidal drugs. We can only hope that still better disease-modifying therapies for conditions such as osteoarthritis are in the offing, so that someday we will be able to offer our patients not just relief from symptoms, but actual remission of disease.