New evidence of over-marketing of Vioxx and other anti-inflammatory drugs

Joseph Kay
16 February 2005

The case of Vioxx calls attention to an important feature of the pharmaceutical industry in the United States: the vast amounts of money spent on marketing drugs. Hundreds of millions of dollars are spent to promote "blockbuster" drugs, which are essential for maintaining the profits of the major drug companies. What should be a scientific question—whether a drug should be provided to a particular patient to help meet a particular illness or disease—is thoroughly corrupted by the influence of money.

With Vioxx, the excessive marketing and sale of the drug appears likely to have contributed to thousands of deaths. Vioxx was withdrawn from the market by its manufacturer, Merck, in September 2004 after the company's own internal study provided strong evidence that the drug caused serious heart problems in many patients. One estimate of excessive cases of serious heart conditions caused by Vioxx, published in an article by Dr. David Graham in the medical journal *The Lancet*, puts the figure at 80,000 to 140,000.

Vioxx is part of a class of drugs known as COX-2 inhibitors, which were developed during the 1990s to treat inflammation. The class of drugs also includes Celebrex and Bextra, both of which are manufactured by Pfizer. The drugs were heavily promoted as a means of treating arthritis without causing the gastrointestinal problems sometimes associated with traditional medications such as ibuprofen and naproxen (Aleve), collectively known as non-steroidal anti-inflammatory drugs (NSAIDs).

All of the COX-2 inhibitors have come under scrutiny for possibly causing heart problems, though only Vioxx has been withdrawn from the market. No evidence has shown that these drugs are more effective in alleviating inflammation than traditional medications. The main group of people that should be prescribed the drugs—if they should be prescribed at all—is the class of patients with a high risk of experiencing gastrointestinal problems associated with NSAIDs.

However, according to a recent study published in the January 24 issue of the *Archives of Internal Medicine*, most of the growth in COX-2 prescriptions from 1999 to 2002 went to patients with a low risk of gastrointestinal problems.

The study is called "National Trends in Cyclooxygenase-2 [COX-2] Inhibitor Use Since Market Release" and was authored by doctors Carolanne Dai, Randall Stafford and G. Caleb Alexander. It used data from two national surveys that sampled patient visits and the prescriptions that patients received. These surveys did not provide data beyond 2002, so the authors do not draw any conclusions about prescription data for the past three years.

The authors noted that "the public health benefit of COX-2 inhibitors depends on their use in patients at higher than normal risk from NSAIDs." However, "increases in COX-2 inhibitor use among patients in whom NSAIDs could be used [i.e., people with a low risk of gastrointestinal problems] accounted for more than 63% of the growth in COX-2 inhibitor use during the period examined."

Overall, when one of the two classes of drugs—COX-2 inhibitors or NSAIDs—was prescribed, the percentage of COX-2 prescriptions increased from 35 percent in 1999 to 61 percent in 2002. "Among patients with the lowest risk for adverse events from NSAIDs, the proportion receiving a COX-2 inhibitor increased from 12% in 1999 to 35% in 2002," write the authors.

The authors conclude, "There is no doubt that, based on currently available evidence, some fraction of patients will benefit from COX-2 inhibitors.... While it may be difficult to estimate this fraction, it is likely to be far lower than the 61% of patient visits with receipt of a COX-2 inhibitor rather than NSAID in 2001 and 2002."

According to the authors, the percentage of the population that is at a high risk of suffering from the side effects of NSAIDs is fairly low, at about 2 percent. The much more expensive COX-2 inhibitors—the authors note that "the wholesale price of COX-2 inhibitors is markedly greater than that of NSAIDs"—could never have become the blockbuster drugs that they did become through prescriptions only to this layer of the population.

Why this "non-selective" use of COX-2 inhibitors, prescribing them to patients who could have received the

same benefits from using cheaper, safer drugs? The authors point to a number of possible factors, including the tendency to assume that newer drugs are more effective than older treatments. “In addition,” they note, “the impact of marketing and promotional efforts must also be considered. COX-2 inhibitors have been heavily promoted, both through direct-to-consumer advertising as well as to physicians. For example, in 2000, Vioxx...was the most heavily advertised direct-to-consumer drug with expenditures of $161 million.”

The *Archives of Internal Medicine* article does not examine in detail the character of this marketing; however, a February 11 report in the *New York Times* describes some of the methods used by Merck to promote Vioxx.

In “Marketing of Vioxx: How Merck Played Game of Catch-Up,” authors Barry Meier and Stephanie Saul, citing internal company documents, describe how Merck aggressively funded doctors who the company thought favored prescribing Celebrex over Vioxx. “In the ‘neutralize’ documents written by a Merck marketing executive,” the authors write, “company officials identified dozens of influential but ‘problem’ physicians.... To win them over, the documents show, Merck officials planned to offer them carrots like clinical trials, posts as consultants or give them grants.”

The documents suggest that Merck saw the funds provided to these doctors essentially as bribes to convince them to prescribe Vioxx. One document spoke of the “Expected Outcome/Return on Investment” from the “neutralizing” activity.

One doctor targeted by Merck was Roy Altman. According to the *Times*, “At a dinner that year [1999] in Miami, a Merck executive asked Dr. Altman what it would take to win his support, the doctor recalled. Dr. Altman said he told the executive that he wanted to run a clinical trial involving Vioxx, and, later, Merck put up $25,000 for it. ‘Show me the money,’ appeared on an internal Merck document near Dr. Altman’s name.”

Another was Max Hamburger, a rheumatologist in Melville, New York. A Merck memo notes that Dr. Hamburger was seeking funding from drug companies to pay for a retreat for a group of doctors that he led. At the retreat, the doctors were planning on establishing guidelines for prescribing different drugs. The Merck memo states, “Companies that provide funding will receive preferred status with [the group’s] members and those that do not will have trouble accessing” it. The “Price tag is $25,000,” according to the memo.

Both the doctors deny that the funding they received from Merck affected their prescriptions practices in any way.

Even as Vioxx and the other COX-2 inhibitors were being heavily promoted, no systematic studies were carried out—either by the companies or the US Food and Drug Administration (FDA)—to determine whether they were safe. An accompanying editorial in the January 24 edition of the *Archives of Internal Medicine* referred to a recent study demonstrating that evidence of the cardiovascular risk of Vioxx was available at least as early as 2000, and yet no action was taken by either Merck or the FDA to follow up on this evidence. “Even if the initial signal of increased cardiovascular risk seen in VIGOR [an early trial conducted by Merck] may not have warranted immediate curtailment of the drug’s use, it surely warranted aggressive and timely follow-up by both the FDA and Merck, including new clinical trials specifically targeting this question.”

Not only were no trials specifically targeting the safety of Vioxx carried out, but Merck cancelled one that had been prepared. A February 8 article in the *Times*, also by Barry Meier, describes a trial that was designed by doctors at the Cleveland Clinic.

At first, Merck agreed to carry out the study into whether Vioxx might increase heart attacks among certain high-risk patients. The study was set to begin in early 2002. However, in March of that year, company executives shut down the trial, just days before the trial’s protocol was due to be submitted to the FDA. At the time, Merck was in negotiations with the FDA over what warnings would appear on the drug’s labels. The drug was withdrawn after a second study, one designed to examine potential benefits associated with the drug, produced strong evidence that it caused heart attacks.