

Patients, Doctors Agonize Over Risks of Painkillers

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Lori Rubinstein, a 47-year-old Manhattan executive, considered Vioxx a godsend.

"It was the most wonderful thing that had come along" to treat her fibromyalgia, a debilitating disorder marked by full-body pain, stiffness and fatigue.

Then Vioxx was taken off the market by its maker because it doubled the risk of heart attack and stroke. Rubinstein moved to the next option in the same family of drugs, Celebrex — just in time for a study showing that it increased the risk of heart problems even more than Vioxx did.

And if that weren't enough, on Monday, the National Institutes of Health said that it had found a similar, albeit smaller, risk with Aleve. The drug, which contains a form of naproxen, is a member of an even more widely used class of painkillers.

In light of this new data, patients are flooding their physicians' offices with questions — and physicians are not sure how to respond.

"It's a complete mess," said Dr. P.K. Shah, a cardiologist at Cedars-Sinai Medical Center in Los Angeles. "The story is really muddy."

In the space of a few weeks, a scientific pall has been cast over the two major categories of painkillers, drugs that are taken by tens of millions of people on a routine, even casual, basis.

Popular Medicines

The most widely used drugs are the nonsteroidal anti-inflammatory drugs, or NSAIDs, a family that includes aspirin, ibuprofen and naproxen, among others.

Most have been used for decades and provide significant pain relief, but they have the capacity to induce serious bleeding problems in the stomach and intestines. Perhaps as many as 20% of the people who need pain relief are not able to take NSAIDs because of this problem, according to Dr. Steven Richeimer, director of

pain medicine at USC's Keck School of Medicine.

The second group, which includes Vioxx, Celebrex and Bextra, are known as Cox-2 inhibitors. They were introduced in the late 1990s to provide the pain-relieving effects of NSAIDs without producing bleeding problems.

The Cox-2 inhibitors quickly became blockbuster drugs, even though some studies showed that they didn't always prevent bleeding in the stomach or intestines.

The health risks associated with all of the drugs are relatively small, perhaps much lower than their benefits for many patients.

In a study designed to determine whether Vioxx could prevent colon cancer, researchers found 25 heart attacks and strokes among 1,299 patients receiving a placebo, compared with 45 among 1,287 patients receiving Vioxx.

In a similar study with Celebrex, researchers found six heart attacks or strokes among 667 patients taking placebos, compared with 35 among 1,333 patients taking Celebrex. Researchers have not released comparable numbers for naproxen, but said that it increased the risk by 50%.

All of the studies in which increased risks were observed involved long-term, persistent use of the drugs at relatively high doses.

For some patients with serious health problems, the decision of what to do hasn't been that hard.

Roger Boesche, 56, of Los Angeles said he wasn't bothered by the increased risk.

"I don't worry about reading in the paper that Celebrex doubles my chance of a heart attack or stroke, because I wonder what's my chance to begin with," said Boesche, a political scientist at Occidental College who has suffered from rheumatoid arthritis for 40 years.

Boesche was taking Celebrex, aspirin and several other drugs to control his pain when he developed serious ulcers in 2003 and had to stop taking all drugs for eight weeks. "I really felt it; it was really painful," he said.

He is now taking just Celebrex.

Dr. Mark Horowitz of the Mt. Sinai Medical Center in New York agreed that the Cox-2 inhibitors had a role to play.

"Certain groups of patients with autoimmune illnesses like rheumatoid arthritis or lupus will always be candidates for these medications, because the alternatives for them are going to have their own inherent risk," he said. "It would be a pity if these

drugs were taken off the market."

Painful Decision

But for those who are more at risk for heart trouble because of age or previous health problems, the decision is literally painful.

Rita Werner, 72, has had osteoarthritis for 40 years and began taking Celebrex soon after it came out because she was suffering from indigestion associated with her NSAIDs.

In 1999, the professor of English at Los Angeles Valley College had a mild heart attack. Because of her past condition, her doctor has now taken her off all pain medication.

He told her to take an NSAID if the pain gets really bad.

For the moment, most physicians are probably telling their patients something very similar to the advice rendered by USC's Richeimer.

"I'm telling patients there may be some risks to [the Cox-2 inhibitors]," Richeimer said. "If they are only getting mild or moderate benefit, they should consider other things. If they are getting great benefit and have no cardiovascular history or risks, I'm willing to prescribe them as long as they understand the risks."

But, he added, "That advice may be very different in just a few weeks."

The science of painkillers has seemed to get only muddier as the controversy wears on.

A major study published in the Archives of Internal Medicine this month showed that abruptly halting the use of naproxen and other so-called NSAIDs increased the risk of having a heart attack within the next 30 days by 50%, especially in patients with rheumatoid arthritis or lupus.

If the new data are true, this seems like a case of "damned if you do and damned if you don't," Shah said.

Another confusing piece is that some doctors and researchers question the results of the study on naproxen.

The data on naproxen have not been completely analyzed, the presence of possible confounding factors has not been studied and it is not clear whether the apparently increased risk is statistically significant.

Conflicting Data

More important, the finding contradicts earlier studies which found that naproxen not only presented no increased risk, but that it actually conferred protection, reducing heart attack risk by 15% to 20%, Shah said.

"There is no recognized feature of naproxen action that could explain these apparent findings," said Dr. Garret A. FitzGerald of the University of Pennsylvania Medical School, a longtime critic of the Cox-2 inhibitors. "An increase in risk is not only counterintuitive as we understand the mechanism, but also contrary to epidemiological analyses of our experiences to date, which suggest a mild protective effect."

In contrast, physicians have a readily accepted mechanism for how Cox-2 inhibitors increase risk — by interfering with enzymes that inhibit the clotting of blood within arteries.

"It is fair to say that the evidence for the Cox-2s is not very favorable," Shah said. "The evidence for the NSAIDs is not very compelling — certainly not yet."

However the story turns out, some researchers think the uproar has at least gotten doctors and patients to rethink the routine use of such drugs, which can be costly — and sometimes unnecessary.

"One of the few silver linings to this whole incredible story is that it has allowed doctors to talk about whether patients need NSAID therapy at all," said Dr. A. Mark Fendrick of the University of Michigan. "It allows us to remember nondrug therapies such as exercise and physical therapy, and other non-NSAIDs such as acetaminophen."

Many people give short shrift to the old standby acetaminophen — most widely recognized as Tylenol — which provides pain relief even though it doesn't reduce inflammation.

"People tend to discount Tylenol quite quickly," Fendrick added. "What you have to remember is that the benefits of Tylenol over nothing are far greater than the benefits of NSAIDs over acetaminophen."

Times staff writer Ricardo Alonso-Zaldivar contributed to this report.