



Drug warnings outline danger

By Rita Rubin, USA TODAY

When the Food and Drug Administration wants to get a message across loud and clear about a prescription drug's risk, it tells the manufacturer to add a black-box warning to the label.



Several high-profile drugs in recent months have been given new black-box warnings — named for the narrow outline of a rectangle that surrounds their boldface text.

But some observers suggest that the federal agency may be relying too heavily on the label warnings and accompanying printed materials.

And some question whether, in the case of at least one drug, the FDA went overboard, preventing patients who could benefit from getting a prescription.

Recent FDA decisions to add black-box warnings have generated a good deal of publicity:

- Antidepressants now warn of a possible link to suicidal behavior.
- Prescription non-steroidal anti-inflammatory drugs (NSAIDs), a group of pain relievers that includes ibuprofen and naproxen as well as the blockbuster Celebrex, will have to carry a black-box warning highlighting the increased risk of heart attacks, strokes and bleeding of the digestive tract.
- At the recommendation of an advisory panel in February, the FDA is working on a black-box warning for Elidel and Protopic, two eczema creams linked to cancer in animals.

When pharmacists dispense these drugs, they'll hand out consumer-friendly MedGuides explaining risks and benefits.

The FDA uses such tools to ensure that the only patients who take potentially dangerous drugs are those for whom the benefits outweigh the risks. But even FDA officials acknowledge that they really don't know how effective black-box warnings and MedGuides are in maximizing safe prescribing.

"You know, evaluations of the effectiveness of any of these programs are really limited," Ann Trontell, deputy director of the agency's Office of Drug Safety, told an FDA advisory panel in February.

Clearly, the track record of black-box warnings, MedGuides and "Dear Health Care Professional" letters — often sent to doctors and pharmacists when a new warning is added to a drug label — is uneven.

"There are a lot of examples that, at best, don't provide you with much reassurance that labeling changes work," Alastair Wood, a pharmacologist at Nashville's Vanderbilt University and chairman of the NSAIDs advisory panel, said at the February meeting. "That is not to say we shouldn't do them, but certainly, just labeling changes on their own have not been extraordinarily effective."

The antihistamine Seldane, pain reliever Duract, heartburn drug Propulsid and diabetes drug Rezulin all came off the market because multiple revisions in their labels failed to adequately reduce what the FDA considered inappropriate prescribing.

There do appear to be some success stories, depending on your perspective. Safety concerns led GlaxoSmithKline in 2000 to stop selling Lotronex, approved for women with diarrhea-predominant irritable bowel syndrome. Two years later, the FDA took the unprecedented step of allowing it back on the market, but with a 21-line black-box warning and a new risk-management program.

Appropriate candidates

Before doctors can prescribe Lotronex, they must attest that they have the necessary knowledge to diagnose patients and treat them with the drug. They then receive stickers to place on prescriptions, confirming to pharmacists that a patient is an appropriate candidate for the drug.

Far fewer doctors prescribe the drug now than before it came off the market, says Elizabeth Andrews of the Research Triangle Institute in North Carolina. Andrews, a former Glaxo scientist, is now lead investigator on a Lotronex patient survey.

"Is that program so restrictive that patients who really could benefit aren't?" Andrews asks. "The patients who have the most severe symptoms are the only ones getting the drug."

Ketorolac, an NSAID for moderately severe pain, carries a black-box warning against taking it for more than five days because the risk of drug-related liver problems rises over time. According to an August 2004 memo from FDA officials Mark Avignan and Gerald Dal Pan, the average length of prescriptions for ketorolac was a fairly consistent five to seven days over the five-year period ending in May 2004.

Still, the authors acknowledged, they did not know whether the drug's labeling deserved all the credit for the short-term prescribing. Health plan reminders that excess days on ketorolac wouldn't be covered also might have prompted pharmacists to dispense the drug frugally.

The FDA does not have the authority to dictate medical practice, only to influence it, points out Robert Temple, associate director for medical policy at the FDA's Center for Drug Evaluation and Research.

"I think sometimes people just don't agree with you," Temple says. "There's a recommendation (a boldface but not boxed label warning) for periodic liver testing for all the statins, and I don't think

everybody's doing that.

"You could probably have a debate about whether it's really worth it," he says. "They might be right, they might be wrong."

Cholesterol-lowering statins present a relatively low risk of liver problems compared with, for example, Rezulin. What Temple says really worries him is when doctors ignore warnings about clear, severe risks. "That's a different problem," he says. "They're just not getting the message."

In the three years Rezulin was on the market (1997-2000), the manufacturer distributed four "Dear Doctor" letters to licensed U.S. physicians about labeling revisions. But Pamela Heaton, assistant professor of pharmacy practice at the University of Cincinnati College of Pharmacy, calls such letters "probably a relatively ineffective way to get a message across to physicians. They're just getting lost in the shuffle of business."

Heaton is the co-author of a study in the January issue of *Pharmacoepidemiology and Drug Safety* that focused on Ohio Medicaid claims for Rezulin prescriptions.

Before the first "Dear Doctor" letter was sent, about 9% of patients who received Rezulin prescriptions had their liver enzymes checked first. After the first two letters went out, that proportion peaked at 26%. But after the fourth letter went out, the percentage of patients who had their liver enzymes tested before starting treatment actually dropped, to 18%.

"I don't think black-box warnings are going to be any more effective than 'Dear Doctor' letters," says the study's lead author, Robert Cluxton Jr., an associate professor of pharmacy practice and family medicine at the Cincinnati pharmacy college.

Cluxton says the FDA needs to be more proactive to counter drug company marketing. "Even if the FDA would just go to the major (medical) meetings — like go to the major arthritis meetings — and do a special session," he says. "Physicians want to understand what is going on. They just don't want a very brief message: 'You should do this because we think so.'"

Physicians are only one part of the problem, Heaton and Cluxton say. "From my perspective, we need to get people other than the doctors involved in this," Cluxton says. "It's got to be the pharmacist, and it's got to be the patient."

Not only do physicians need to be ordering the necessary tests to monitor drug safety, Heaton says, but "we need pharmacists to be asking patients if they've had these tests done. And we need patients to realize if the physician ordered the test, they need to get the test done."

A need for discussion

Simply handing patients a MedGuide might not be enough, says Lee Rucker of AARP's Public Policy Institute. "I think sometimes what's missing is that it's all just on the paper," Rucker says. "There seems to be a need for that face-to-face discussion before the patient is sent out the door."

Negative publicity, as opposed to the new black-box warning, may make patients and doctors more cautious about NSAIDs, says Arthur Levin, the only member of the FDA advisory panel to vote in favor of taking Celebrex off the market.

"I don't think this will be a true test, frankly, of the benefits or lack thereof of increasing warning labels," says Levin, director of the New York-based Center for Medical Consumers. "It's hard for

people to understand that something can be approved, can be advertised, can be prescribed for you by a doctor and still not be safe."

