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The Last Word on FDA Opioid Labeling?

PROP, PROMPT still disagree; REMS revisions next

by Donald M. Pizzi

The FDA has modified the safety labeling for extended-release (ER) and long-acting (LA) opioid analgesics, as well as required further postmarketing studies to be conducted by the manufacturers of the agents. Although many of the changes reflect requests made in a petition from a physicians' group looking to limit the prescribing and use of opioids for safety reasons, many of the group's recommendations were not adopted by the FDA.

The drug labeling sections that are affected include Dosage and Administration, Warnings and Precautions, Drug Interactions, Use in Specific Populations and Patient Counseling Information, as well as the Medication Guide.

"The labeling changes demonstrate the FDA's resolve to reduce the serious risks of long-acting and extended-release opioids while still seeking to preserve appropriate access for those patients who rely on these medications to manage their pain," FDA Commissioner Margaret A. Hamburg, MD, said in a statement.

According to Douglas Throckmorton, MD, deputy director for regulatory programs in the FDA's Center for Drug Evaluation and Research, the new labels "describe more clearly the risks and safety concerns associated with ER/LA opioids and will encourage better, more appropriate prescribing, monitoring and patient counseling practices involving these drugs."

Chief among the Physicians for Responsible Opioid Prescribing's (PROP) requests that were included in the new labeling is language stating that opioids should not be prescribed for moderate pain. The updated labeling states that ER/LA opioids are indicated "for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate." Another major addition to the labeling is the inclusion of a boxed warning on the risk for neonatal opioid withdrawal syndrome associated with chronic use during pregnancy.

In a press statement on its website, the FDA stressed the need for individualized treatment for

chronic pain patients, and that the new labeling is designed to help health care professionals reach these goals with each of their patients. “The updated indication further clarifies that, because of the risks of addiction, abuse and misuse, even at recommended doses, and because of the greater risks of overdose and death, these drugs should be reserved for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated or would be otherwise inadequate to provide sufficient management of pain; ER/LA opioid analgesics are not indicated for as-needed pain relief,” wrote the FDA in the statement.

Lynn Webster, MD, president of the American Academy of Pain Medicine, said he was in favor of the new labeling that reserves opioid use for patients in severe pain who require long-term treatment. The change, he explained, “will take into account factors other than a pain scale score that should be considered when prescribing opioids.”

PROP Requests Left on Table

Andrew Kolodny, MD, president of PROP, tempered his happiness about the labeling changes with frustration regarding changes that were not made. “We [PROP] were pleased, but we feel that FDA should have gone much further,” he said. “Their decision to exclude IR opioids is baffling, because all the risks are the same. We’re [also] disappointed that they didn’t add a suggested maximum duration of use of 90 days and a maximum dosage of 100 mg morphine equivalents. We wanted use beyond these parameters to remain an option for physicians and patients, but we wanted it to be off-label because risks of long-term and high-dose use are likely to outweigh benefits for most chronic pain patients.”

Dr. Webster said the labeling changes marked “a good day for people in pain who find opioids helpful. The FDA did a careful and thoughtful review of the petition presented by Physicians for Responsible Opioid Prescribing and decided there was not enough evidence to support most of the arguments made in the petition.”

More Research, Changes To REMS

In addition to the labeling changes, the FDA announced new postmarketing clinical study requirements focusing on “the known serious risks of misuse, abuse, increased sensitivity to pain (hyperalgesia), addiction, overdose, and death.” Dr. Webster described the FDA’s requirement for manufacturers of opioids to conduct long-term safety and efficacy studies as “long overdue.”

After final labeling is in place, the FDA intends to revisit the ER/LA opioid analgesics’ Risk Evaluation and Mitigation Strategies (REMS) program that was approved in 2012, “to reflect the updated information.” The current REMS mandates that the manufacturers of ER and LA opioid analgesics provide training for health care professionals who prescribe these agents, as well as educational materials for the health care professionals and for their patients that explain how to safely use the medications.

PROMPT Founder Responds

Jeffrey Fudin, PharmD, FCCP, the chairman and founder of Professionals for Rational Opioid Monitoring and Pharmacotherapy (PROMPT), a multidisciplinary group of 35 physicians, pharmacists and other pain specialists, said the majority of members were pleased with the FDA's conclusions. "The way we see it, the agency carefully reviewed thousands of submitted documents and scientific literature in support of and in opposition to the proposed label changes," he said. "Their findings and final ruling fits squarely with FDA REMS insofar as it relates to ER/LA opioids. Essentially all of PROP's unsubstantiated assertions were appropriately denied."

Dr. Fudin added that the new label regarding pain levels—"severe enough to warrant around-the-clock opioids"—is more patient-friendly than previous labeling "because it doesn't require a visual analog scale that is very subjective," he said. "Instead, it tells us that 'severe enough' is dependent on patients' needs if around-the-clock dosing is required daily in order for the patient to function."

Dr. Fudin said he disagreed with some of the more stringent labeling requests that have been made. He noted, for example, that "the FDA had no supportive evidence to set a 100 mg (or other) morphine-equivalent dose, and even if they did, there is no uniformly accepted equivalence on which clinicians consistently rely. Moreover, if there were such an acceptable equivalency, it still doesn't account for inter-patient variability, genetic polymorphisms and drug interactions, all of which could have a profound effect on opioid dose conversions."

He added that the FDA "aptly denied an arbitrary 90-day opioid limit" for chronic non-cancer pain (CNCP). "Imagine all of the patients with CNCP who have pain 'severe enough to warrant around-the-clock opioids' who would have fallen outside of the proposed label changes," he said. "Some include those with arachnoiditis, cystic kidney disease, [and] Ehlers-Danlos syndrome, and cancer survivors for whom the line is no longer so clear of what constitutes malignant versus non-malignant pain." Moreover, "the FDA made it quite clear in their Sept. 10 response letter that they knew of no physiologic or pharmacologic basis upon which to differentiate the treatment of chronic pain in a cancer setting or patient from the treatment of chronic pain in the absence of cancer." Comments to the petition docket, he added, "reflect similar concerns."

The FDA's decision, Dr. Fudin said, "was based on available evidence; it responsibly correlated with their REMS [Risk Evaluation and Mitigation Strategies] initiative and was sympathetic to the vast majority of legitimate chronic pain patients and the clinicians who care for them. To quote Dr. Bob Twillman from the Feb. 7, 2013, FDA hearings held in Bethesda, Md., 'the absence of evidence is not evidence of absence.'"

—Additional reporting by David Bronstein

As Opioid Scrutiny Grows, Will Risks Posed by NSAIDs Be Overlooked?

In the wake of FDA changes to labels for extended-release/long-acting opioid pain relievers, clinicians and patients may be looking elsewhere for ways to manage moderate pain. Non-steroidal anti-inflammatory drugs (NSAIDs) offer a potential alternative, but some clinicians are urging that a possible increase in NSAID consumption should be met with caution.

"We hope the impact will not be great," said Daniel Brzusek, DO, vice chair of the Alliance for Rational Use of NSAIDs. "But we think that not only physicians but the lay public will rely on NSAIDs."

According to Michael Carome, MD, director of Public Citizen's Health Research Group, it's "hard to say" if the new FDA labeling will influence NSAID use. He cited the variety of pain relief options that could be used in lieu of opioids or NSAIDs. "Non-NSAIDs, like Tylenol, may be reasonable for some patients," said Dr. Carome. "And frequently, these are underutilized."

Both Dr. Carome and Dr. Brzusek mentioned there are ways to relieve pain that do not rely on pharmaceuticals, such as exercise and behavioral therapy. Dr. Brzusek also cited acupuncture as "a safer, zero-risk alternative" to NSAIDs.

In the United States, an estimated 23 million people use NSAIDs for daily pain relief. Though considered safe when used properly, these drugs may result in adverse effects such as cardiovascular events and gastrointestinal (GI) bleeding. A recent meta-analysis of the adverse effects of NSAIDs found that, compared to placebo, for every 1,000 patients per year receiving a coxib or diclofenac, there would be three additional vascular events, of which one would be fatal. The meta-analysis also reported an increase in upper GI complications compared to placebo—most frequently, bleeding—at rate ratios of 1.81 for coxibs (P=0.0070), 1.89 for diclofenac (P=0.0106), 3.97 for ibuprofen (P<0.0001) and 4.22 for naproxen (P<0.0001) (*Lancet* 2013;382:769–779).

Patients who use NSAIDs should take the "least dose possible for the shortest period of time," Dr. Brzusek said. "That's a maximum of 10 days." Dr. Brzusek begins with a minimal dose—for example, 200 mg ibuprofen three times daily, 75 mg diclofenac daily or 250 mg naproxen twice daily—and titrates up the dosage every three days until there is no additional positive response.

How big a problem NSAIDs pose is a matter of debate. In September, Lynn Webster, MD, president of the American Academy of Pain Medicine, told *Pain Medicine News*, a sister publication to *Pharmacy Practice News*, that "deaths from GI bleeding linked to NSAIDs rival deaths from opioids, according to some estimates." This statement provoked a strong response from Andrew Kolodny, MD, president of Physicians for Responsible Opioid Prescribing, who wrote on Twitter that Webster's remark was "false" and should be corrected.

Estimates of deaths due to GI bleeding range from a high of 16,500 (*J Rheumatol Suppl* 1999;56:18-24) to a more conservative 2008 report from the Centers for Disease Control and Prevention, which cited 3,400 deaths. In contrast, the CDC recorded 14,800 deaths from opioids in 2008.

When asked about the number of deaths from NSAIDs compared with the number of opioid-related deaths, Dr. Brzusek said he doesn't believe deaths from NSAIDs are quite so high. "There are definitely a lot of deaths from bleeding," he said, "but hospitalizations are more common." According to the Alliance for the Rational Use of NSAIDs, NSAIDs contribute to at least 100,000 hospitalizations per year.

Dr. Carome emphasized that he is not opposed to the reasonable administration of NSAIDs. "All drugs have problems," he said. "Patients need to be made aware of that."

—Ben Guarino