American Society of Anesthesiologists

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April 8, 2013

Margaret Hamburg, M.D.
Commissioner
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket No. **FDA-2012-N-1172**; Impact of Approved Drug Labeling on Chronic Opioid Therapy

Dear Commissioner Hamburg:

The American Society of Anesthesiologists (ASA), on behalf of over 50,000 members, is writing in response to the Food and Drug Administration (FDA) Federal Register notice regarding the public workshop on the impact of approved drug labeling on chronic opioid therapy. ASA offers the comments below in regards to the petition to change the label of opioid analgesics submitted by Physicians for Responsible Opioid Prescribing (PROP). The petition requests that the FDA:

1) Strike the term "moderate" from the indication for non-cancer pain.
2) Add a maximum daily dose, equivalent to 100 milligrams of morphine for non-cancer pain.
3) Add a maximum duration of 90-days for continuous (daily) use for non-cancer pain.

As the medical specialty representing the largest number of practicing pain medicine physicians and the recognized leader in patient safety, ASA has significant interest in reducing the misuse, abuse, and diversion of opioid medications that have led to unintended deaths. ASA supports the broad concept that high dose opioids should not be used to treat chronic non-cancer pain. However, placing specific limits on daily doses of opioids that a physician may prescribe is not scientifically founded nor is it practical.

One of the basic facts that pain educators teach new students is that there is wide variation between individuals in the intensity of pain experienced from apparently identical surgical operations, trauma, or chronic medical conditions with comparable pathology. Another basic truth is that there is substantial inter-individual variation in the response to analgesic agents, particularly opioids. As a therapeutic class, opioids encompass a range of molecular structures whose interactions with an array of receptors and metabolic pathways are highly diverse. At present, translational research is dramatically advancing our knowledge of the genetic bases underlying diversity in every aspect of nociception, pain, and the response to pain therapies. Yet amidst this exciting progress, PROP's petition for uniform limits on doses and duration of treatment ignores the importance – and real therapeutic promise – of individualized medicine informed by advances in preclinical science. Because the petition ignores a complex reality, its provisions if adopted would immediately raise numerous practical difficulties for physicians and patients.

A fundamental flaw shared by all three components of the PROP proposal is the intrinsic difficulty in defining "non-cancer pain." Improvements in cancer therapy have resulted in increases in survival duration as well as cure rates, although the treatments used to achieve these beneficial results often lead to chronic pain. Who will decide whether the persistent pain, for example, of herpes zoster or nerve damage incurred during an otherwise curative course of chemo- and radiation therapy is or is not cancer-related?

In regards to the first proposed change, it is very common for pain intensity to fluctuate during long-term treatment of chronic non-cancer pain. Pain that is moderate at one time may be severe a few hours later, and then decline to become moderate shortly thereafter. Pain that is moderate at rest typically increases to severe when the patient undertakes desirable physical activity. Hence, patients are often instructed to self-medicate with an opioid shortly before anticipated physical activity in order to keep their pain from becoming severe. It would not be practical to instruct patients never to take an opioid during intervals when their pain is moderate, but only to do so when their pain is severe.

In addition, pain intensity is assessed as a patient-reported surrogate for a subjective experience. Hence, the proposed wording would be unenforceable. Everyday clinical assessment of pain intensity typically employs a 0-10 scale in which "moderate" pain is identified with values of 4, 5 or 6. Imagine a physician telling a patient that because the patient reported his or her recent pain intensity as a "6" out of 10, i.e., moderate, the new label would not support – nor might an insurer pay for – continuing chronic opioid therapy. On the other hand, had the intensity been reported as "7" out of 10 there would be no problem prescribing the medication. How many patients might then say, well, on second thought it actually was closer to a "7" than a "6"?

The proposed wording is also silent as to what proportion of the time pain would need to be reported as "severe" in order to justify prescribing an opioid. A clinical trial involving such an approach to pain therapy would not be approved by a human studies committee. In addition, if a patient started opioid therapy when pain was "severe," but pain intensity decreased to "moderate" as a result of the medication, would the label refer to the time before or after the patient started opioid therapy? How would one approach the management of a patient whose pain intensity had been stable at a mild or moderate level while on chronic opioid therapy, but then increased to severe whenever the opioid dose was tapered? This typical scenario illustrates the practical difficulty of implementing the proposed label change. All of the preceding points relate back to a basic principle of pain management, that the optimal treatment regimen should be designed to keep pain well-controlled, i.e., to prevent pain from becoming severe.

Regarding the second proposed change, considerable clinical experience attests to substantial inter-individual differences in the analgesic effect of morphine and other opioids. The population-based conversion factors used to calculate "equivalent" morphine doses in patients treated with non-morphine opioids differ from patient to patient, and even in the same patient followed across time (e.g., with declining kidney or liver function, or dehydration). Patients who require higher doses of opioids as a result of their individual genetics might well argue that implementation of this proposed change represents unfair discrimination, and deemed illegal just as unfair and prejudicial discrimination on the basis of gender or race would be.

In regards to the third proposed change, opioids for moderate pain, high dose opioids, or opioids taken for longer than 90 days may be effective for certain patients and should continue to be a treatment option if clinically appropriate. An example would be for the patient with a chronic painful condition who does not tolerate NSAIDs or for whom they are contraindicated, and for whom other non-opioid treatments have been inadequate. The petitioners set strict limits on dose and duration of opioid therapy for non-cancer pain based upon group statistics. However, just as it is illogical to generalize observations from a single patient to guide the treatment of an entire group of patients, the converse is also true. One cannot use population-based, aggregate epidemiological findings to set specific limits that are valid for every patient, given the inter-individual differences in pathophysiology and opioid responsiveness of seemingly identical chronic non-cancer pain conditions.

ASA advocates for an approach more flexible than the strict limits requested in the petition. The petitioners use epidemiologic data to draw conclusions as to dosage and duration that would more appropriately be presented as guidelines, not mandates, for the treatment of large unselected populations

such as are seen in primary care. Moreover, pain treatment physicians see complex patients who by definition are selected outliers whose problems have persisted or worsened during non-specialist care. Mandating rigid, across-the-board limits on opioid dosage and duration would add difficulty to our already-challenging task of caring for this subgroup of outlier patients.

ASA strongly believes that access to opioids must be balanced with efforts to reduce the misuse, abuse, and diversion of these medications. Federal and state governments, health care professionals, law enforcement, and other stakeholders are implementing initiatives to curb prescription drug abuse while maintaining patient access to the medications they need. ASA has had the pleasure to work with stakeholders on these initiatives, which include health care professional education, Risk Evaluation and Mitigation Strategies (REMS), prescription drug monitoring programs, and medication storage and disposal.

ASA also agrees with many in the pain treatment community that additional research should be conducted on the long-term efficacy of opioids for chronic pain. Fundamental questions bearing upon the benefit-to-risk ratio of opioids and other treatments for chronic non-cancer pain must be resolved, such as the percentages of patients of various ages and genders who will become tolerant, dependent upon, or addicted to opioids during long-term therapy. This effort must be accomplished in a comprehensive fashion, accommodating individual variability and the diversity of our nation's population, and supplementing results from randomized controlled trials with outcomes data on treatment effectiveness in everyday settings of care. We understand that such studies are now being planned with FDA support, as their results will provide a scientific basis to inform public policy and regulatory actions.

We look forward to continue working with the FDA on this important issue. Please feel free to contact Lisa Pearlstein, J.D., Pain Medicine and Regulatory Lobbyist at l.pearlstein@asawash.org or 202-289-2222 if you have any questions or need additional information regarding this issue.

Sincerely,

John Zerwas, M.D.
President
American Society of Anesthesiologists