Risk Evaluation and Mitigation Strategy for Extended-Release And Long-Acting Opioids: Clinicians Weigh In

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In 2012, the FDA approved a Risk Evaluation and Mitigation Strategies (REMS) program for extended-release and long-acting opioid (ER/LA) analgesics. The current REMS mandated that the manufacturers of ER/LA opioids provide voluntary 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. *Pain Medicine News* asked clinicians with a strong focus on pain medicine to comment on the REMS a year later.

What are your general feelings about the approved REMS for opioids? Do you feel they have made an impact clinically?

Lynn R. Webster, MD, *President, American Academy of Pain Medicine, and medical director, CRI Lifetree Research, Salt Lake City, Utah*

My view is that responsible physicians welcome the development of educational programs to assure safe use, along with the creation of safety-related materials to educate patients. Educating patients concerning the proper use, storage, and disposal of the opioids that are prescribed to them is important to reducing the diversion of medications into the wrong hands. I also find it appropriate that industry is called on to financially support the educational initiatives that spread information about the safe use of its products, yet does not control the content of the programs.

Clifford Gevirtz, MD, *Medical director, Somnia Pain Management, Office Based Anesthesia/ Ambulatory Surgery Group Louisiana State University New Orleans Health Sciences Center, New Orleans, Louisiana*

I think it has dramatically transformed the opioid-prescribing process for fentanyl for breakthrough pain. REMS has really restricted its use to evidence-based use and not an off-label approach. As a reviewer for several insurance programs, I wondered what these prescribers were thinking in prescribing very high doses of fentanyl with relatively low basal levels of oxycodone or morphine in patients with nonspecific back pain or fibromyalgia.

I think the very concept of breakthrough pain needs to be rethought. Instead of chasing very high-dose, short-acting agents, we need to give more thought to how and when to raise the basal level. Six doses a day of breakthrough medication tells me that the basal level isn't high enough.

I am also very concerned with the cost of fentanyl products. Do we really need to lease our patients a Rolls Royce every month when a Chevy will be just fine? The cost of Fentora lozenges (Teva) can run well over $2,000 a month when Percocet (oxycodone/acetaminophen, Endo) costs just pennies a dose.

Christopher Gharibo, MD, *Assistant Professor of Anesthesiology & Orthopedics, and Medical Director of Pain Medicine, Hospital for Joint Diseases, Department of Anesthesiology, New York University Anesthesia Associates, New York*

The current REMS model of strongly encouraging clinicians to educate themselves will be largely ineffective. Many clinicians do not have the time or the motivation to undergo such an educational program, although they may be completely lacking formal training.

Many clinicians feel that their patients, practice, and communities do not have an opioid problem to address. Other clinicians may overcompensate and stop prescribing altogether.

The truth is somewhere in the middle. Opioids are an important tool in our clinical armamentarium and although they may be lacking long-term evidence, so does just about every other analgesic out there.

Opioid prescribing is mechanism-based and can be a helpful part of an overall balanced analgesic plan.

Opioid prescribing is not just about selecting the low-risk, suitable patient but also about realizing that psychological risk is constant and dynamic, and the pharmacologic plan always needs to have strategies that maximize multimechanistic efficacy and compliance while keeping the pill counts as low as possible and encouraging proper safeguarding pill bottles as much as possible.

David S. Craig, PharmD, *Director, Pain and Palliative Care Specialty Residency, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida*

I have mixed feelings on the final product. Like many others who were part of the many opioid REMS FDA advisory committees, I strongly feel that the program should do more—specifically cover the entire drug class and require mandatory prescriber education. Additionally, I felt that it was a perfect opportunity to improve the way pain was managed within the United States while reducing harm, but many of the necessary elements were left out of the final product. To have any effect, this type of "risk mitigation" strategy must be mandatory for all prescribers, and it must have clear and measurable outcomes that really do something like improving patient safety and prescriber knowledge. I am not opposed to any continuing medical pain education surrounding the effective use of opioids, but feel that this program could have gone further. I feel that this was a missed opportunity.

Lewis S. Nelson MD, *Professor of Emergency Medicine, and Director, Fellowship in Medical Toxicology, New York University School of Medicine, New York City Poison Control Center, New York*

The FDA is in the difficult position of assuring the availability of safe and effective medications, while addressing the perceived needs of patients and providers in the absence of convincing evidence. The FDA is appropriately taking "baby steps" while sequentially assessing the effects of its efforts. One palpable benefit of the new REMS is the use of a classwide approach, eliminating the confusion of a related but subtly distinct REMS for each individual product. I am, however, concerned about the reliance on voluntary education to improve safety and appropriate prescribing. Although education is absolutely essential, it has generally proven insufficiently successful as a primary approach in the vast majority of prior public health efforts, such as smoking and seatbelt use. Furthermore, although few in clinical medicine feel that more "merit badges" are optimal, the likelihood that voluntary medical education would be sought out and accepted seems very low.

Is there anything you feel could or should have been addressed in the guidelines but wasn't?

Dr. Gevirtz: The required frequency of urine toxicology and what constitutes informed consent for opiates.

Dr. Craig: Again, this REMS for ER/LA opioids should have included the entire class of opioids—immediate release (IR) and extended/long acting—and mandatory prescriber education. Additionally, it should have gone further to reduce potential harm to patients by including more on opioid abuse risk stratification techniques and psychological dependence.

Dr. Nelson: There are several adverse outcomes from liberal opioid prescribing: addiction in an individual, diversion to others, abuse with subsequent overdose, and therapeutic safety even if used "correctly." Given these and possibly other concerns, a broad-based and aggressive strategy that relies on more than education of what is "right" is going to be essential. For example, adding the requirement to either document a risk assessment for medical and psychiatric factors or to access a prescription drug monitoring program before prescribing would help identify patients potentially at risk for overdose, in need of substance abuse counseling, or for participating in drug diversion. Additionally, the omission of a REMS for short-acting opioids is a conspicuous oversight given that the majority of both prescriptions and adversities occurs with these agents. It is interesting that the REMS for the IR transmucosal fentanyl products, which are far less commonly used, is significantly more stringent.

Dr. Webster: I would like to see the medical education component specifically emphasize the risks in prescribing methadone, which is involved in one-third of opioid-related overdose deaths but accounts for only 2% of prescriptions written. Another top safety concern is the coprescribing of benzodiazepines and other central nervous system depressants along with opioids. My hope is that as research continues to accumulate on these problems, creators of the educational programs will respond by incorporating and stressing that content.

Are there any areas where you feel REMS did not go far enough?

Dr. Nelson: Although continuing medical education programs for health care providers offer a needed service, their beneficial effect on patient care is predicated on adherence to high standards of honesty and balance. The excellent "Blueprint for Prescriber Continuing Education Program" from the FDA clearly delineates the content of an educational program, but it leaves it open to the producer to determine the details and tone of the program. The accrediting body of CME [continuing medical education] providers appropriately requires an arm's-length relationship between funders of CME and those who offer these programs. However, a system that removes any relationship between these 2 parties and dispenses educational funds through a truly independent body (such as the FDA) would produce a truer firewall against financial influence. Under such an arrangement, groups that are not necessarily viewed as favorable to opioid analgesic prescribing, but that have a valid perspective (such as those interested in addiction), would be more likely to obtain such educational funds.

Because the risk for adversity from opioid therapy is probably greater than for most medical interventions, requiring informed consent and patient–provider agreements merits inclusion. The patient counseling document and medication guide, which are intended to be educational tools for patients, are each missing important safety data. There is a "write-in" option on the counseling document, but this is likely to be minimally effective.

An alternative approach to baby steps is to implement a mandatory, aggressive REMS and scale back the requirements as more is learned. Review of the model developed for buprenorphine to treat opioid addiction may be informative. Although this is a drug with better safety and proven efficacy compared with analgesic opioids, mandatory certification and a limit on patient volume are involved. Regardless, the key to the successful balance of safety and effectiveness is serial outcome assessment and revision of the REMS process.

The FDA is newly empowered to require postmarketing study of the effectiveness and safety of opioid analgesics in both high-dose and long-term dosing regimens. Because pharmacotherapy is often driven by the availability of medications, a critical question that needs to be addressed is in which patients (and what "diseases") do the significant risks truly outweigh the benefits of this known, dangerous, but theoretically beneficial, class of medications. Given the vagaries of the diagnosis of pain, particularly chronic pain, and the substantial perverse incentives that clinicians face, impartial guidelines, perhaps funded or produced by FDA, would be a welcome addition for safety.

Dr. Gharibo: Omission of short-acting opioids from the REMS was a mistake. Many patients and clinicians start the problem by over-relying on short-acting opioids for subacute/subchronic pain for constant, daily pain. Once you dig your patient into that hole, getting out of it can be a challenge because the patient develops pill-taking behavior, psychodynamic effects of quick onset, and end-of-dose withdrawal that can largely be mitigated by ER/LA opioids. The REMS program needed to put IR, ER and LA and their proper use into better perspective.

Dr. Webster: Should REMS training, for example, have been made mandatory for all clinicians who prescribe extended-release opioids? Yes, I think so. I would prefer the education to be voluntary, but mandatory education may be necessary, particularly because our medical schools and residency programs are not providing adequate education on safe prescribing.

I also would have supported a REMS for other opioid formulations. However, the measured approach taken by the FDA could have far-reaching and spillover benefits in which education for extended-release opioids could improve practices for short-acting opioids, too. If 60% of opioid prescribers can be reached within 3 years—the goal that the FDA has set—that would be a significant start. Whether the White House Office of National Drug Control Policy (ONDCP) can reach its goal of a 15% decline in unintentional overdose deaths remains to be seen. That will take a coordinated effort by many other entities—federal, state, local, public, and private—of which REMS is only a part.

Dr. Gevirtz: Short-acting medications like Percocet and Norco (hydrocodone/acetaminophen, Watson) also need some form of REMS. There has been a huge increase in overdoses and deaths due to prescription opiates, and why and how they are prescribed needs to be carefully addressed. I think the Washington state requirement of having a pain management review of patients on high-dose opiates is really the way to go, along with statewide registries that have to be checked before any prescription being written.

Do you think REMS has in any way created a barrier between chronic pain patients and appropriate pain treatment?

Dr. Webster: It is my view that REMS sets forth minimum safety standards and that we should embrace that intent, collectively working toward safe use of all opioids, not just extended-release opioid formulations. It is possible that REMS will reduce the number of people receiving opioids, but that may be considered a positive development, reflecting more judicious prescribing that screens out people who are unlikely to benefit from opioid therapy. At the same time, inattention to chronic pain treatment is indeed prevalent in our society, a reality that was highlighted by the Institute of Medicine in its report on pain in America. The goal of safe and effective use must not contribute to this societal pattern. Professionals and advocates in the pain field should continue to push for access to appropriate treatment for all patients suffering from pain, including nonopioid, evidence-based alternatives and opioids, when opioids are the right treatment. I see this as a transformational opportunity for our specialty.

Dr. Craig: No, I don't think this program has or will create any barriers for chronic pain patients and appropriate treatment because, as it exists, this program doesn't require prescribers to do anything new or different. However, I do hope that at some point state medical and professional licensing boards will make some level of pain management education and risk mitigation education—like the one approved REMS for ER/LA opioids—a requirement for licensure.

Dr. Nelson: Just the opposite. Because the majority of chronic pain is managed by primary care and other "non–pain medicine" physicians, providing a basic set of ground rules, even if imperfect, is a start toward improved care. There is nothing in the current REMS that prevents a clinician from prescribing acute or chronic opioid therapy for any patient in any manner. However, given the lack of evidence for the safety and effectiveness of chronic opioid therapy for most patients (and evidence that shows neither), creating a speed bump may be appropriate.

Dr. Gharibo: No, because the program has been ineffective.

Dr. Gevirtz: The only barrier is in physicians' minds. During Prohibition, physicians were able to prescribe alcohol for medicinal purposes and many docs succumbed to the monetary temptations that were presented. I fear that the pill-mill phenomenon is a replay of that time period. We need to tighten up the process to prevent abuse.