Scientists Probe Ways to Curb Opioid Abuse Without Hindering Pain Treatment

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RESEARCH ON THE USE OF OPIOID pain medications is beginning to provide some guidance on curbing abuse of these powerful prescription drugs while allowing patients in need to receive adequate treatment for pain.

Greater recognition of the importance of pain management has led to skyrocketing numbers of prescriptions for opioid analgesics. At the same time, abuse of these drugs has increased (Kuehn BM. *JAMA*. 2007;297:249-251). This pair of trends has left many physicians considering the best ways to ensure that patients get needed pain relief while preventing abuse of pain medications.

To help advance research and interdisciplinary dialogue on the interface between pain treatment and abuse of pain medications, clinicians, scientists, and other stakeholders gathered in March for a conference on this topic sponsored by the National Institute on Drug Abuse at the National Institutes of Health, in Bethesda, Md. Among the presentations were sessions outlining current research on ways to identify patients with substance abuse problems, techniques for safe prescribing, and drugs in development that may offer less addictive alternatives to existing treatments for pain.

A STRUCTURED APPROACH

Prescription opioid abuse is a systemic problem, with failures to recognize and prevent potential abuse occurring at many points in the system—from development and distribution of the pain medications, to the physician's office, and even to the patient's home. Physicians alone cannot solve the problem, but they can take steps to reduce problems at the patient-physician interface, said Nathaniel P. Katz, MD, an analgesic researcher at Tufts University School of Medicine in Boston.

"The first thing physicians need to do is set up systems in their offices that support safe prescribing," Katz said. Such systems should include use of tamper-proof prescription pads, quantitative urine analysis for all long-term opioid analgesic patients at each visit, use of state prescription monitoring data for each patient when available, and addiction screening for all patients followed by intervention and/or referral when appropriate, he said.

Steven D. Passik, PhD, a psychologist at Memorial Sloan-Kettering Cancer Center in New York City, said physicians should establish structured monitoring for their analgesic patients, starting with an assessment of their risk of developing a substance abuse problem. Previous substance abuse problems are often linked with abuse of prescription analgesics, he said. A study that compared pain treatment outcomes in 73 patients with AIDS-related pain and a history of substance abuse and 100 patients with cancer pain and no history of substance abuse verified this link (Passik SD et al. *Clin J Pain*. 2006;22:173-181). The study found that the patients with a history of substance abuse were more than twice as likely to report aberrant drug-taking behaviors than the patients without such a history.

Physicians should triage patients into appropriate treatment regimens based on their risk of developing an addiction, he said. For example, patients at low risk of addiction might be prescribed a long-acting opioid analgesic to control chronic pain and a short-acting analgesic to be used at their discretion to control breakthrough pain, and they may be asked to undergo infrequent urine tests. High-risk patients would be required to have frequent urine tests and would likely receive only a long-acting analgesic.

FREQUENT ASSESSMENTS

All patients taking prescription analgesics should be regularly assessed for effectiveness of treatment and the presence of negative outcomes. Passik and his colleagues have developed a validated assessment tool, the Pain Assessment and Documentation Tool (Passik SD et al. *Clin Ther*. 2004;26:552-561).

It measures outcomes in 4 domains, or the "4 *A*s," reflecting whether patients are receiving adequate *a*nalgesia, experiencing improvements in psychosocial function or *a*ctivities of daily life, experiencing any *a*dverse effects, and persistently participating in *a*berrant medication-taking behaviors that may be linked to addiction.

If such assessments reveal patients are not responding well in any of these domains, it gives physicians an opportunity to intervene and adjust their treatment regimens. This is particularly important for the 30% to 40% of patients who do not respond to opioids. For patients who initially do not respond, Katz said, physicians may want to adjust their dosing regimen, add another analgesic, send the patient to physical therapy, get a psychological consultation, or try another opioid. If the patient still does not respond to additional measures, the physician may try nonpharmacological therapies such as rehabilitation therapies, physical modalities such as ice or heat, psychological therapies such as cognitive behavioral therapies, or complementary medicine, he said. Katz said these therapies, whether used alone or as adjuncts to medication, are evidence-based and efficacious. However, they are less commonly used, in part because they are less aggressively marketed and may not be covered by insurance.

When physicians identify a patient who is exhibiting aberrant drug-taking behaviors, they should try to determine why, Passik said. Such patients may have an addiction; they may not be getting adequate pain relief taking the drug as prescribed; they may have a comorbid mental illness; or they may intend to distribute pain medications illegally.

Passik explained that nonadherence is common among pain patients, with 1 study showing 45% of patients taking opioids for noncancer pain having some nonadherent behavior in the previous 6 months (Passik SD et al. *J Opioid Manag*. 2005;1:257-266). Most of these individuals have just a few episodes of inappropriate medication use and will correct their behavior if their physician talks to them about it. Those who persist despite their physician's recommendations may indeed be abusing their medication. Given these data, Passik said, "1 strike out" policies in which physicians refuse to treat a patient after a single infraction are not warranted.

NEW APPROACHES

Other scientists are optimistic that the development of opioids with less abuse potential and the use of technology to better track opioid drugs may provide physicians with additional tools to prevent abuse of these drugs.

Pamela P. Palmer, MD, PhD, director of the University of California-San Francisco PainCARE-Center for Advanced Research and Education, explained that many existing opioid analgesics have poor bioavailability when ingested, requiring pharmaceutical companies to load very high doses of drugs into oral formulations. For example, oral morphine is only 30% bioavailable, so drug companies must put 3 times as much drug as the patient needs into a dose. That means patients intent on abuse can receive roughly 3 times the intended dose if they crush, dissolve, and inject the drug, which is 100% bioavailable intravenously.

The problem is compounded in extended-release formulations of short-acting opioid drugs. A half-day's or a full-day's worth of drug, multiplied to offset limited oral bioavailability, may be loaded into a single extended-release pill. If the pill is crushed and then snorted or injected, an individual would receive many times the intended dose.

Using opioid drugs or formulations with higher bioavailability, ideally 100%, would reduce this potential for abuse, Palmer said. Additionally, the use of drugs that are naturally long-acting for long-acting formulations would eliminate the need to load large amounts of a short-acting drug into an extended-release formulation.

"We need to work with the chemistry of the drug and route of administration to make sure we are optimally packaging these drugs to prevent abuse," she said.

Some scientists and drug companies are already developing more abuse-resistant products. Palmer has worked with AcelRX Pharmaceuticals Inc, based in Redwood City, Calif, to develop a tiny sublingual sufentanil pill that has more than 90% bioavailability and dissolves almost instantly in the mouth. Even when the pill is crushed, the dose is unchanged, she said. Other scientists working with Durect Corporation, based in Cupertino, Calif, have developed an abuse-resistant oxycodone extended-release gel capsule, which cannot be circumvented by crushing the capsule, heating it, or mixing it with alcohol. It is in late-phase clinical trials.

Another strategy drug companies are exploring is adding opioid antagonists such as naloxone or naltrexone to opioid pain medications, she said. These drugs may block the pleasant effects of taking opioids or elicit unpleasant effects when the drug is abused.

Palmer said better tracking of how patients are taking their drugs might also be helpful. For example, AcelRX Pharmaceuticals has developed an electronic pill dispenser for its sublingual sufentanil pills that would keep track of when patients dispense their medication and how much they use. Physicians could ask their patients to bring the dispenser to appointments and download the usage record.

KNOWLEDGE GAPS

Many crucial questions about the long-term effects of prescription opioid medications remain unanswered, such as whether the drugs remain efficacious, what the adverse effects are, and the rates of abuse and addiction in pain patients over time, Katz said.

"There are a lot of things we don't know about opioids, and there are a lot of things we do know but can't implement," Katz said. Physicians interested in helping patients with chronic pain should support

legislation aimed at boosting insurance reimbursements for nondrug pain treatments, encourage funding agencies to back practical clinical studies, and help develop straightforward, evidence-based guidelines for opioid prescribing, he said.

Despite the need for more information and some of the continuing challenges for physicians treating patients with chronic pain, many speakers emphasized that physicians must continue to treat pain aggressively.

"Aggressive pain management is here to stay," Palmer said. "It's up to the pharmaceutical industry, the biotech companies, and physicians to be smarter about prescription opioids used for pain management." □