New drug-delivery systems make it more difficult to extract or manipulate active ingredients.

BY KERRI WACHTER
FROM THE ANNUAL MEETING OF THE AMERICAN ACADEMY OF PAIN MEDICINE
NATIONAL HARBOR, MD – Pharmaceutical companies are stepping up to address increasing opioid abuse and misuse by developing innovative abuse-deterrent formulations and drug delivery systems, Dr. Lynn R. Webster said.

Dr. Webster discussed several new opioid formulations that are currently available and some promising technologies in the pipeline. Dr. Webster is board certified in anesthesiology and pain medicine and is certified in addiction medicine. He is also the medical director and founder of the Lifetree Clinical Research and Pain Clinic in Salt Lake City.

New Opioids
In January 2011, the Food and Drug Administration approved Abstral (Prostrakan), a fentanyl transmucosal tablet indicated for the management of breakthrough cancer pain in adults. As an alternative to oral tablets or injections of fentanyl pain medications, the quick-dissolving tablet is placed under the tongue, providing very fast relief for cancer-related pain in patients already receiving opioids for pain treatment.

Approved in 2010, Exalgo is an extended-release formulation of hydromorphone indicated for once-daily administration for the management of moderate to severe pain in opioid-tolerant patients who require continuous, around-the-clock opioid treatment for an extended period. Exalgo (Mallinckrodt) is not intended for use as an as-needed analgesic. The formulation utilizes a new osmotic, controlled-release oral delivery system in which osmosis attracts water in the body to the inside of the capsule to trigger release of hydromorphone. It takes about 6 hours for effective levels of hydromorphone to be released and 4–5 days for drug levels to reach a steady state in the body, Dr. Webster said.

There has been a resurgence of interest in buprenorphine. This drug has been around for several decades, but is now being used to treat chronic pain. Buprenorphine is a partial mu-opioid agonist, an antagonist at the kappa-opioid receptor, and a partial agonist at the ORL1/nociceptin and delta-opioid receptors. “This is a little bit of complexity with how the pharmacology of this drug works. We probably don’t understand clinically what all of that means yet,” Dr. Webster said.

Buprenorphine is the only opioid classified as a schedule III drug, making it an attractive choice for pain management. Buprenorphine also is associated with fewer of the side effects typical of opioids, such as respiratory depression.

In 2010, the FDA approved Butrans, an extended-release buprenorphine patch (Purdue Pharma), in 5, 10- and 20-mcg/hour doses. The drug is indicated for the management of moderate to severe chronic pain in patients requiring continuous, around-the-clock opioid treatment for an extended period. Notably, Subutex (buprenorphine monotherapy) and Suboxone (a buprenorphine/naloxone combination product) are approved for use in opioid addiction treatment, though other forms of the drug are not. However, other forms of buprenorphine are commonly used off label for the management of addiction disorders, Dr. Webster said. Because buprenorphine is an opioid partial agonist, its maximal effects are less than those of full agonists (like heroin and methadone). At low doses, buprenorphine is thought to produce enough of an antagonist effect to enable opioid-addicted individuals to discontinue the misuse of opioids without experiencing withdrawal symptoms. Buprenorphine has poor oral bioavailability and only moderate sublingual bioavailability.

In the Pipeline
Acurox (Acura Pharmaceuticals and King Pharmaceuticals) is an oral immediate-release oxycodone tablet with a proposed indication for the relief of moderate to severe pain. Acurox is formulated so that if the tablets are dissolved in an attempt to extract the opioid for intravenous injection, the tablets turn into a viscous gel mixture with the active drug trapped in the gel. The Aersion technology used also caus es burning and irritation of the nasal passages and the drug is crushed and inhaled.

Last year, the FDA rejected an application for a version of the drug containing naiacin, which was formulated so that the uncomfortable “niacin flush” would deter overuse of the drug. In February 2011, the FDA accepted a new drug application for Acurox (oxycodone) tablets without niacin.

MoxDuo (QRxPharma) is an immediate-release dual opioid intended for the acute management of moderate to severe pain. The drug is a combination of oxycodone and naloxone, a drug clinically shown to have a synergistic effect on pain with a significant reduction of total opioid dose and side effects.

“This formulation is built upon that thought that there are different receptor selectivities to an opioid,” Dr. Webster said. “Because opioid receptors differ, you can get enhanced analgesia with using overall less morphine equivalents, or you could get fewer side effects with the same level of analgesia, when you combine two different opioids.”

Collegium Pharmaceuticals is developing an abuse-deterrent, sustained-release oral oxycodone formulation (COL-003). The DETERx delivery technology consists of a multiparticulate matrix formulation in a capsule designed to be less susceptible to common forms of tampering, such as crushing and chewing prior to ingestion. Company studies showed that the plasma profile for the new-formulation pill was bioequivalent whether it was chewed or taken whole as intended. “It’s an abuse-resistant formulation in that they can’t extract more than is intended for its delivery,” Dr. Webster said.

Remoxy (Pain Therapeutics and King Pharmaceuticals) is a long-acting oral oxycodone for the treatment of moderate to severe chronic pain. This is what I consider an opioid-resistant formulation, meaning it’s got a barrier that is hard to crush, hard to manipulate; and it’s’ hard to extract” the oxycodone, Dr. Webster said. “It can’t be chewed, snort ed, or injected very easily.”

A new transmucosal buprenorphine patch is also in the trial phase. According to PharmacomFore, the delivery system’s developer, the novel Bio-Activated Molecular Delivery (Bio-MD) technology deters prescription drug abuse at a molecular level.

“This technology does not involve the reformulation of existing opioid drugs in physical matrices that are easily circumvented by simple extraction methods. Our opioid Bio-MD systems are ‘activat ed’ to release clinically effective opioid drugs only when exposed to the correct physical and chemical stimulation,” the company noted on its Web site.

Essentially, an opioid molecule – any opioid – is attached to the delivery compound. “It’s kind of like a clock. The intrinsic tripwin in our GI tract will activate that clock, which will allow that drug to be released,” Dr. Webster said. The clock determines how much time it takes for the active compound to be released. “It’s very early on,” he cautioned. “The delivery system is in phase 1 trials. Still, “it looks very interesting that they have the technology now to address multipill abuse. There are ways to design the same technologies so that the triggering system will only allow a certain number of pills or milligrams of medication to be absorbed.” Thus, regardless of how many pills an individual takes, no more than the correct amount is bioavailable.

Dr. Webster reported that he has significant financial relationships with a number of pharmaceutical companies, including King Pharmaceuticals and Collegium Pharmaceutical.

Offerings in Pipeline to Tame Opioid Abuse

European Panel Weighs Options for NSAID Treatment

BY ESTHER FRENCH
FROM ANNALS OF THE RHEUMATIC DISEASES

A panel of 18 experts from 10 European countries had some difficulty in defining when the benefits sufficiently outweighed the potential adverse effects of various NSAIDs – with and without a proton pump inhibitor – for 144 profiles of patients with chronic rheumatic diseases.

Panels had difficulty giving patients with low gastrointestinal or cardiovascular risks the full range of NSAID options. Approximately one-third of the patients are assigned “inappropriate” by panels applied to the use of a nonselective NSAID without a PPI (Ann. Rheum. Dis. 2011;70:818-22).

When scoring patient profiles, panels took into account several clinical variables: age of 65 years or older, history of gastrointestinal problems, use of anticoagulants, use of low-dose corticosteroids, intermittent or continuous treatment pattern, cardiovascular risk, and the use of low-dose aspirin (for those patients with cardiovascular risk). Against these variables, panels considered 10 treatment options: ibuprofen, diclofenac, naproxen, meloxicam, celecoxib, etoricoxib alone or in combination with a PPI (proton pump inhibitor), or a nonselective NSAID plus PPI were considered appropriate. In cases of high gastrointestinal risk and low to average cardiovascular risk, panels rated ibuprofen/diclofenac plus PPI, or a COX-2 inhibitor plus PPI, as the most appropriate options. For patients with both high gastrointestinal and cardiovascular risks, avoidance of all NSAIDs was recommended, with the use of diclofenac, naproxen, celecoxib, or etoricoxib plus PPI deemed as the most appropriate option.

In January 2008, the panel established the appropriateness rating of treatment options on a 1-9 scale, with 1 as “inappropri ate” and 9 as “appropriate.” As defined by the RAND/UCLA appropriateness method, a treatment had to be considered appropriate if the expected benefits exceeded the potential negative consequences by a sufficient margin.” However, the panel rated this “sufficient,” which led to most of the disagreement on scoring.

All panels disclosed receiving honoraria from Pfizer, which supported the study with a research grant. Eleven panels disclosed other relationships with pharmaceutical companies, including Pfizer.