Scientists identify drug to treat opioid addiction

February 17 2009

Scientists at Stanford University School of Medicine have discovered that a commonly available non-addictive drug can prevent symptoms of withdrawal from opioids with little likelihood of serious side effects. The drug, ondansetron, which is already approved to treat nausea and vomiting, appears to avoid some of the problems that accompany existing treatments for addiction to these powerful painkillers, the scientists said.

Opioids encompass a diverse array of prescription and illegal drugs, including codeine, morphine and heroin. In 2007, about 12.5 million Americans aged 12 and older used prescription pain medications for non-medical purposes, according to the National Survey on Drug Use and Health, administered by the federal government's Substance Abuse and Mental Health Services Administration.

"Opioid abuse is rising at a faster rate than any other type of illicit drug use, yet only about a quarter of those dependent on opioids seek treatment," said Larry F. Chu, MD, assistant professor of anesthesia at the School of Medicine and lead author of the study that will be published online Feb. 17 in the *Journal of Pharmacogenetics and Genomics*. "One barrier to treatment is that when you abruptly stop taking the drugs, there is a constellation of symptoms associated with withdrawal." Chu described opioid withdrawal as a "bad flu," characterized by agitation, insomnia, diarrhea, nausea and vomiting.

Current methods of treatment are not completely effective, according to

Chu. One drug used for withdrawal, clonidine, requires close medical supervision as it can cause severe side effects, while two others, methadone and buprenorphine, don't provide a satisfactory solution because they act through the same mechanism as the abused drugs. "It's like replacing one drug with another," said co-investigator Gary Peltz, MD, PhD, professor of anesthesia.

"What we need is a magic bullet," said Chu. "Something that treats the symptoms of withdrawal, does not lead to addiction and can be taken at home."

The researchers' investigation led them to the drug ondansetron, after they determined that it would block certain receptors involved in withdrawal symptoms.

The scientists were able to make this connection thanks to their having a good animal model for opioid dependence. Mice given morphine for several days develop the mouse equivalent of addiction. Researchers then stop providing morphine to trigger withdrawal symptoms. Strikingly, these mice, when placed into a plastic cylinder, will start to jump into the air. One can measure how dependent these mice are by counting how many times they jump. Like humans, dependent mice also become very sensitive to pain when they stop receiving morphine.

But the responses vary among the laboratory animals. There are "different flavors of mice," explained Peltz. "Some strains of mice are more likely to become dependent on opioids." By comparing the withdrawal symptoms and genomes of these different strains, it's possible to figure out which genes play a major role in addiction.

To accomplish this feat, Peltz and his colleagues used a powerful computational "haplotype-based" genetic mapping method that he had recently developed, which can sample a large portion of the genome

within just a few hours. This method pinpoints genes responsible for the variation in withdrawal symptoms across these strains of mice.

The analysis revealed an unambiguous result: One particular gene determined the severity of withdrawal. That gene codes for the 5-HT3 receptor, a protein that responds to the brain-signaling chemical serotonin.

To confirm these results, the researchers injected the dependent mice with ondansetron, a drug that specifically blocks 5-HT3 receptors. The drug significantly reduced the jumping behavior of mice as well as pain sensitivity — two signs of addiction.

The scientists were able to jump from "from mouse to man" by sheer luck: It turns out that ondansetron is already on the market for the treatment of pain and nausea. As a result, they were able to immediately use this drug, approved by the Food and Drug Administration, in eight healthy, non-opioid-dependent humans. In one session, they received only a single large dose of morphine, and in another session that was separated by at least week, they took ondansetron in combination with morphine. They were then given questionnaires to assess their withdrawal symptoms.

Similar to mice, humans treated with ondansetron before or while receiving morphine showed a significant reduction in withdrawal signs compared with when they received morphine but not ondansetron. "A major accomplishment of this study was to take lab findings and translate them to humans," said principal investigator J. David Clark, MD, PhD, professor of anesthesia at Stanford University School of Medicine and the Palo Alto Veterans Affairs Health Care System.

Chu plans on conducting a clinical study to confirm the effectiveness of another ondansetron-like drug in treating opioid withdrawal symptoms in

a larger group of healthy humans. And the research team will continue to test the effectiveness of ondansetron in treating opioid addiction.

The scientists warned that ondansetron will not by itself resolve the problems that arise with continued use of these painkillers. Addiction is a long-term, complex process, involving both physical and psychological factors that lead to compulsive drug use. "This is not a cure for addiction," said Clark. "It's nad've to think that any one receptor is a panacea for treatment. Treating the withdrawal component is only one way of alleviating the suffering. With luck and determination, we can identify additional targets and put together a comprehensive treatment program."

Source: Stanford University Medical Center