The Search for an Ideal Analgesic:
Lessons from the NIH Medicines Development Program
Tufts Health Care Institute Program on Opioid Risk Management
Boston, Massachusetts
May 4-5, 2012

HIGHLIGHTS

- The National Institutes of Health (NIH) analgesics development program was started in the 1930's during the epidemic of morphine abuse in the U.S. From 1930 to 2007, the program evaluated new opioid agonists and antagonists that revolutionized the practice of pain medicine and saved many lives by enabling substance abuse treatment. The closing of this program in 2008 is a terrible loss for science and for medicine.
- Participants in the Tufts Health Care Institute (THCI) summit meeting unanimously agreed that the NIH analgesics development program must be promptly revived to enhance the development of safer and less "abusable" analgesic medications, in order to curb the current epidemic of prescription opioid abuse.

EXECUTIVE SUMMARY

Pain has recently been described by the Institute of Medicine as a $500 billion problem that affects over 100 million Americans. Prescription opioid abuse costs over 15,000 lives annually, with its own costs approaching $100 billion. Complications associated with non-steroidal anti-inflammatory drugs (NSAIDs) result in high morbidity and mortality.

The epidemic of morphine abuse and addiction at the turn of the 20th century prompted the government to start a research program, ultimately at NIH, which aimed at developing non-addictive pain medications. The federally funded NIH analgesics development program was set up as a "three-legged stool" with the major components being a medicinal chemistry center, an animal testing center, and a human testing center in Lexington, KY, which later moved to Baltimore.

While the program did not find the "holy grail," enormous accomplishments in the history of medicine were made by this program, including the development of most of the opioids and opioid antagonists used in modern medicine. Some of the program's accomplishments were the development of methadone, LAAM, buprenorphine, tramadol, naloxone, naltrexone, and fentanyl. These medications have tremendously improved the practice of medicine today, and have improved and saved many lives by allowing more effective treatment of pain, substance abuse, and opioid overdose. The NIH program was quietly shut down in February 2008 because

of the lack of funding for drug testing, despite the renewed epidemic of morbidity and mortality due to analgesic use, from not only opioids but NSAIDs and acetaminophen.

On May 4 and 5, 2012, the THCI Program on Opioid Risk Management convened a summit meeting in Boston to better define the need for safer analgesic medications and to develop recommendations to address it. The meeting was co-chaired by Nathaniel Katz, MD, MS and Frank Vocci, PhD.

While the pharmaceutical industry is eager to develop and commercialize better analgesics, most of its efforts have been targeted at reformulating existing analgesics to make them more convenient or less "abusable." Only a few pharmaceutical companies are currently developing analgesics targeting mechanisms or pathways that are not related to the opioid receptors, such as the FAAH enzyme or the cannabinoid receptors. Although this effort may bear fruit in the long-term, it is not sufficient in the context of the current epidemic of prescription opioid abuse and the associated morbidity and mortality. Currently, the NIH budget devoted to chronic pain research represents less than two percent of the total NIH budget, and only one-tenth of the NIH neuroscience budget.

The summit meeting participants unanimously agreed that the NIH analgesics development program must be revived as soon as possible. Potential components of the revived program could include refunding a network of laboratories to focus on medicinal chemistry, refunding of animal testing facilities with a focus on developing more predictive animal models of pain and addiction, and setting up a small network of clinical research sites to rapidly and inexpensively screen compounds for analgesic activity and abuse potential. This program will need to fit into the current NIH structure, but must have a strong, independent, and dedicated leadership focused exclusively on the goals of this program, in order not to get lost in the shifting sands of NIH priorities and activities.

Recent discoveries in opioid pharmacology—such as the landmark 2012 crystallization of the opioid receptor and ligands that target mu receptor heterodimers and that may lack the side effects of tolerance and dependence—and discoveries of non-opioid analgesics with powerful analgesic capabilities in animals and humans should create new opportunities to develop better, more targeted analgesics. Thus, the time is right to revive the NIH pain medicine program to fully exploit these new discoveries.