New hope for addicts

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It doesn't take a rocket scientist to quickly grasp what a University of Mississippi professor's research could mean to the millions of people addicted to hardcore narcotics such as heroin, cocaine, methamphetamine and morphine.

School of Pharmacy faculty member Christopher R. McCurdy has made it his mission to find and develop compounds to unlock the shackles that bind people to addictive drugs.

"A lot of people who become addicted to methamphetamine, cocaine or even heroin truly want to quit," McCurdy said. "They begin with recreational use and don't think they will become addicted, but (they) soon get to the point where they almost must take the drug to survive, because withdrawal is so intense."

Making withdrawal more endurable – and therefore, cessation more likely – is the goal of several projects in McCurdy's medicinal chemistry laboratory. Among them is a National Institutes of Health Centers of Biomedical Research Excellence-funded study of kratom, a botanical mixture derived from Mitragyna speciosa, a treelike plant native to Southeast Asia. (COBRE grants are awarded by the NIH's National Institute of General Medical Sciences through its Institutional Development Award, or IDeA, program, which builds research capabilities in states that historically have had low levels of NIH funding.)

"In Southeast Asia, kratom has long been used for coughs, diarrhea, muscle aches and pain," McCurdy said. "It is also used as a replacement for opium when opium isn't available and has been used to wean people off (that narcotic)."

McCurdy and his colleagues made a tea from Mitragyna leaves, freeze-dried it and tested it in mice habituated to morphine. Results indicate the tea has some undesirable side effects but that modifications eliminate them and show great promise.

Taking the work a step further, the group isolated the plant's most abundant alkaloid, mitragynine, and tested the pure compound. Results indicate this compound's activity is superior to methadone in the mouse withdrawal assay and that carefully created chemical variations may provide an alternative to methadone in treating addictions to opiates.

"Mitragynine completely blocked all withdrawal symptoms and could provide a remarkable step-down-like treatment for people addicted to hardcore narcotics such as morphine, oxycodone or heroin," McCurdy said. "The compound has been known for years, but we're working to come up with an improved synthetic analog or a better formulation of the tea for testing in humans."

Collaborating on the study is Dr. Edward W. Boyer, professor of emergency medicine and director of medical toxicology at the University of Massachusetts School of Medicine.

"Dr. Boyer is an opium treatment specialist and, through an anonymous chat room, asked kratom users how much they used, how often they used and whether they had any withdrawal symptoms," McCurdy said. "That information helped us determine dosages and frequencies for our animal studies."

Despite the U.S. Drug Enforcement Administration listing kratom as a "drug of concern" because of its abuse potential and stating there is no legitimate medical use for it in this country, several million Americans purchase kratom on the Internet to self-manage chronic pain and/or opioid withdrawal, and some are ending up in emergency rooms. After one who had been using kratom four times a day for more than three years arrived in the ER with seizures, Boyer sent a sample of the material to McCurdy and his colleagues for analysis. They found no contaminants, which helped determine the seizures resulted from co-administration of modafinil 20 minutes earlier (*Addiction*, 2008, 103, 1048-1050).

Their analysis of material taken by a patient arriving at the University of Colorado ER revealed it was laced with hydrocodone and morphine, and analysis of material taken by a mother giving birth to an opiate-addicted baby at a University of Louisville hospital revealed the material was also laced with hydrocodone.

McCurdy and Bonnie Avery, an Ole Miss associate professor of pharmaceutics who has been instrumental in the analytical and pharmacokinetic analysis of kratom, have become recognized as experts on this plant material. "We can authenticate it and determine when it's adulterated," McCurdy said.

The Mississippi laboratory staff's ability to help answer clinicians' questions is of enormous benefit, Boyer said.

"We have been able to distinguish the effects of kratom from those of other drugs whose presence was unanticipated," he said. "This has allowed us to document that some toxicity of kratom is actually from other pharmaceutical agents that had been added."

Just as promising as the work on kratom is another study funded by the National Institute on Drug Abuse, which indicates several small molecules block the behavioral and toxic effects of cocaine and methamphetamine in animal models by coupling with sigma receptors in the brain. These highly selective compounds have been studied by a group of international collaborators, including McCurdy, Jacques H. Poupaert, a medicinal chemistry professor at the Université Catholique de Louvain in Belgium, Rae R. Matsumoto, associate dean of research and graduate programs at West Virginia's School of Pharmacy, and Frederick T. Chin, head of cyclotron radiochemistry in the Stanford University Medical Center's molecular imaging program.

"No one has been able to block self-administration of cocaine in rats with compounds in this class, but one of our compounds did, and we are excited about publishing these results soon," McCurdy said.

Jonathan L. Katz, chief of the Psychobiology Section of NIDA's Intramural Research Program in Baltimore and his colleague, Takato Hiranita, tested the compound in cocaine-addicted rats.

"When given the drug, the rats stopped taking cocaine," Katz said. "But what makes this drug so interesting is that the drug had no effect in the other activities of the rats. This kind of selectivity is what makes drugs suitable as medicines."

Today, nothing is available to either treat cocaine and methamphetamine addiction or block the seizures and other complications associated with overdoses of drugs with monikers such as crack, crystal methamphetamine and ecstasy.

"This product could potentially be the first of its kind to hit the market," McCurdy said. "There's still a long way to go, but our research team is motivated to complete the preclinical studies necessary to allow us to start doing human studies."

Fred Taylor, an IDeA program official at the NIH's NIGMS, said that the university's COBRE grant "has enabled the University of Mississippi to successfully train and mentor developing investigators, build state-of-the-art research infrastructure and conduct exemplary research activities. In pursuing these goals of the IDeA program, the center is making an impact on biomedical research and health in Mississippi, the region and the nation."

Provided by University of Mississippi