

Disulfiram, Vaccine May Curb Cocaine Addiction

BY BARBARA RUTLEDGE
Contributing Writer

MENDOZA, ARGENTINA — Two promising pharmacotherapies are currently in clinical trials for treatment of cocaine dependence: disulfiram and a vaccine consisting of a cocaine-cholera toxin complex, Dr. Thomas Kosten said at the Sixth World Congress of Depressive Disorders.

Cocaine blocks the reuptake of dopamine, and after chronic abuse it causes a reduction in the number of postsynaptic dopamine receptors and eventually leads to damage of dopamine-responsive cells in the brain, said Dr. Kosten, professor of psychiatry and neuroscience at Baylor College of Medicine, Houston.

Neuroimaging studies show visible changes in the brain after abuse of amphetamines or cocaine, with a noticeable decrease in the number of dopamine-responding cells. Changes persist even after cocaine use has stopped.

"We have done these imaging studies out to 18 months after stopping cocaine and have shown no restoration in function," he said. "It appears that these may be very long-term and relatively irreversible changes."

Disulfiram (Antabuse) may improve this dopamine-deficient state, particularly in people with genetically low levels of the enzyme dopamine beta-hydroxylase, which converts dopamine to norepinephrine. Norepinephrine is associated with withdrawal symptoms, and dopamine is associated with reward from normal activities as well as from drug abuse. Disulfiram inhibits dopamine beta-hydroxylase, causing cells to release dopamine rather than

norepinephrine. In seven placebo-controlled, double-blind studies involving more than 700 patients, disulfiram produced considerably better results than did placebo: up to 55% of urine samples were cocaine free in the disulfiram group, compared with about 40% in the placebo group.

"This is an effect size equivalent to what's seen in antidepressants for treating depression or standard antipsychotic agents for treating schizophrenia," Dr. Kosten said.

The increased amount of dopamine appears to change the acute effects induced by cocaine. Ordinarily, someone smoking cocaine will get euphoria followed by increased craving for cocaine, but disulfiram markedly reduces the craving induced after cocaine is given.

Several minutes after the euphoria abates, the individual is likely to experience cocaine-induced dysphoria, with feelings of nervousness and paranoia that may last for more than an hour. Disulfiram has the dual effect of diminishing the craving and enhancing the negative feelings associated with cocaine use, he said.

Some people experience significantly more nervousness and paranoia when taking disulfiram with cocaine. Genetic mapping has suggested that people who experience disulfiram-induced dysphoria have a dominant mutation in a gene leading to the synthesis of dopamine beta-hydroxylase, a mutation that results in abnormally low enzyme levels. Thus, the dual action of disulfiram has therapeutic implications, particularly in abusers with abnormally low levels of dopamine beta-hydroxylase, who showed the best response to disulfiram treatment, Dr. Kosten said.

The vaccine approach targets the drug itself rather than the receptor. The cocaine molecule is too small to provoke an immunologic response on its own, so the vaccine consists of a complex of cocaine attached to the cholera toxin molecule. Antibodies generated to the cocaine-cholera toxin complex bind to cocaine, trapping it in the bloodstream and preventing its entry into the brain.

Several clinical trials have been conducted, and the vaccine appears to be safe and well tolerated. The most effective dosage is a high dose of the vaccine given five times over a period of 3 months. High levels of antibodies are necessary for a therapeutic effect. The vaccine blockade can be overridden, but three- to fourfold higher levels of cocaine are required for the drug user to feel the "normal" response to cocaine, Dr. Kosten said.

In clinical trials, about 75% of subjects appeared to have an effective antibody response. Subjects who received the vaccine had a significantly higher proportion of cocaine-free urines, compared with baseline, than did subjects who received placebo.

"We will move into phase III [Food and Drug Administration] approval studies in the next year or so, with the hope that this vaccine might be available in 2 or 3 years," he said.

Dr. Kosten reported no conflicts of interest. He does not hold stock in Celtic Pharma, the company developing the vaccine. His studies have been supported by the National Institute on Drug Abuse.

Celtic Pharma has supplied vaccine and has conducted independent monitoring of the clinical trials for potential FDA submission. ■

Methamphetamine Use Adversely Affects Patients, Trauma Centers

BY DAMIAN McNAMARA
Miami Bureau

FORT MYERS, FLA. — Increasing methamphetamine use not only boosts violent injuries and law enforcement altercations among trauma patients, but it can create a significant financial burden for a level I trauma center, according to a study.

Methamphetamine-positive trauma patients were more likely to have a violent cause of injury such as assault, gunshot wound, or stabbing, compared with non-meth users, Dr. Sophia M. Swanson said during poster walk rounds at the annual meeting of the Eastern Association for the Surgery of Trauma.

"Methamphetamine is really increasing nationally," Dr. Swanson said. "An estimated 10 million people have used methamphetamine at least once in their lifetime."

During the 3 years of the study (2003-2005), there was a steady increase in methamphetamine use, from 9% to 15% of patients. Methamphetamine replaced marijuana as the most common drug of abuse in 2005 among patients at the University of California, San Diego, where Dr. Swanson was a medical student at the time of the study.

To gauge methamphetamine's impact, Dr. Swanson and her associates reviewed a registry of 4,648 consecutive trauma patients who had both a blood and toxicology screen at admission. This patient population is the 71% of all trauma patients who had toxicology screens.

"We found meth users were more likely to be young, male, more severely injured, and more likely to be Hispanic," Dr. Swanson said at the meeting, which was jointly sponsored by Wake Forest University.

Methamphetamine users had a higher mean injury severity score (10.9) versus nonusers (9.9); were 56% more likely to require mechanical ventilation; and were 53% more likely to undergo an operation.

The users also were more likely than nonusers to leave the emergency department against the recommendations of physicians (5% versus 2%), and were more likely to die from their injuries (6% versus 3%).

Methamphetamine-positive patients had a fivefold increased likelihood of an altercation with law enforcement. "That is really striking," Dr. Swanson said.

Methamphetamine-positive patients were twice as likely to have violence as the mechanism of injury (47%, versus 26% of nonusers). This finding included 36% more assaults, 85% more gunshot wounds, and 146% more stab wounds than for nonusers.

Adverse effects are not limited to patients. There is an increasingly significant financial burden to trauma centers, Dr. Swanson said. Despite similar length of stays, costs averaged 7% higher for methamphetamine-positive patients. Methamphetamine users were about twice as likely to be uninsured (54% versus 28%). There was an average of \$10,000 of uncompensated care per methamphetamine-positive patient, Dr. Swanson said.

Emergency physicians and trauma physicians can make a difference, Dr. Swanson said. One tactic is screening for amphetamine use and a brief intervention. "It's easy, it's quick, and it can be done in the ED. Lack of reimbursement, however, is a concern." She also recommended that doctors "get involved in community-based methamphetamine prevention programs." ■

Nicotine Patches Found Safe in Coronary Artery Disease Patients

NEW ORLEANS — Nicotine patches are safe for use in smokers with known coronary artery disease and stress-induced myocardial ischemia, according to the results of the first-ever randomized, placebo-controlled, multicenter clinical trial to examine this issue.

Nicotine therapy doubles the



Upon repeat SPECT imaging, the size of the perfusion defects in the patch group was unchanged.

DR. LEJA

successful smoking quit rate to about 30%, but many physicians have been reluctant to recommend it for their patients with coronary artery disease (CAD) because nicotine is known to increase heart rate and blood pressure and can induce vasoconstriction, Dr. Monika J. Leja reported at the annual scientific session of the American College of Cardiology.

She and her coinvestigators at the Methodist DeBakey Heart Center, Houston, therefore randomized 55 heavy smokers with CAD and a quantified 10% or greater stress-induced myocardial

defect by single-photon emission computerized tomography (SPECT) to receive either 21-mg nicotine patches or placebo while continuing to smoke.

The primary end point was change in total perfusion defect size upon repeat stress SPECT imaging at 1 week. There was no change in either the total or ischemic perfusion defect size, compared with baseline in the active- or placebo-patch groups even though plasma nicotine levels in the active-treatment arm jumped from 10.9 to 25.2 ng/mL, Dr. Leja reported.

After 1 week, patients were encouraged to quit smoking while continuing to use their assigned patches.

Upon repeat SPECT imaging at week 4 the size of the perfusion defects in the nicotine patch group remained unchanged from baseline despite the fact that their plasma nicotine levels remained as high as at week 1, lending further support to the safety of nicotine therapy in the CAD population, Dr. Leja said.

The trial was supported by GlaxoSmithKline Consumer Healthcare.

Dr. Leja has no financial relationship to disclose.

—Bruce Jancin