Could a Novel Vaccine Help Smokers Quit?

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"TO CEASE SMOKING IS THE EASIEST thing I ever did. I ought to know because I've done it a thousand times." This popular quote, attributed to Mark Twain, mockingly captures the difficulties of long-term abstinence for nicotine-dependent individuals.

Clinicians have many more tools to treat nicotine dependence than were available in Twain's time. But even though such approaches as nicotine replacement, bupropion, and behavioral therapies have helped many individuals quit, relapse is common.

Some scientists believe that vaccines targeting nicotine may help some individuals kick the nicotine habit. Early clinical trials and basic research on this strategy have yielded some promising results, although many questions remain.

BEATING THE RUSH

Like a conventional vaccine that targets a pathogen, a nicotine vaccine is designed to stimulate the production of antibodies—in this case, nicotine antibodies. The basic premise is that such antibodies might block some of nicotine's reinforcing effects by sequestering the chemical in blood and preventing it from reaching the brain.

Paul Pentel, MD, professor of medicine and pharmacology at the University of Minnesota and director of the division of clinical pharmacology at Hennepin County Medical Center in Minneapolis, said a nicotine vaccine has its greatest effect on nicotine distribution in the body during the first few minutes after a dose of nicotine is administered, when the rewarding effects of smoking are greatest.

A study published online on July 1 in *Psychopharmacology* (http://www.springerlink.com) suggests that this effect may reduce self-administration of nicotine. Mark LeSage, PhD, and colleagues at the University of Minnesota, Minneapolis, found that when rats trained to self-administer nicotine were then injected with a nicotine vaccine, they subsequently used less nicotine. A second group of rats that were vaccinated prior to being trained to self-administer nicotine were no less likely than controls to learn self-administration, but they used less of the drug than unvaccinated control animals.

At the American Society for Clinical Oncology's annual meeting in May, Jacques Cornuz, MD, MPH, head of the Lausanne University Smoking Cessation Clinic in Switzerland, presented results from a phase 2 vaccine trial involving 341 smokers. Participants received either an experimental nicotine vaccine developed by Cytos Biotechnology AG (Zurich, Switzerland) or placebo. The researchers found that individuals who had the highest titers of nicotine-specific antibodies after vaccination were more likely than those treated with a placebo to achieve abstinence; however, there was no apparent difference between vaccinated individuals with lower titers and those who received the placebo.

Kathleen M. Kantak, PhD, director of the laboratory of behavioral neuroscience at Boston University in Massachusetts, said achieving high antibody levels in vaccinated individuals will be key and that more research is needed. "When you vaccinate against a drug of abuse, the antibody levels are extremely variable," Kantak said. "The higher the concentration of antibodies, the better the vaccine will protect against the drug."

So far, the Cytos vaccine, an experimental nicotine vaccine in phase 2 trials that was developed by Nabi Biopharmaceuticals (Boca Raton, Fla), and a third experimental nicotine vaccine in development by the Xenova Group (Berkshire, England), appear to be safe, Kantak said.

However, there are drawbacks to the vaccine approach. For example, vaccines will not necessarily address nicotine withdrawal or cravings; they may work best when used with counseling and possibly in combination with other medications. "Vaccines may turn out to be clinically useful but I wouldn't expect them to address all aspects of tobacco dependence," Pentel said.

One behavioral concern is whether individuals might try to circumvent the vaccine by smoking more, Pentel said. Like other therapies for nicotine dependence, the treatment may only be useful for individuals who are motivated to quit.

Timing of vaccination may also be important, Kantak said, because current smokers have high levels of nicotine in their bodies and very high levels of antibodies are needed to counteract the effects of the drug. Administering the vaccine 2 to 3 weeks after an individual has quit, when the risk of relapse is high, may be more effective than giving it to current smokers.

"If the vaccine were given so that the peak immunity coincides with a time [when cravings start and] the person gives in and has a cigarette and doesn't feel any pleasure from it, they may be

more likely not to continue smoking," Kantak explained.

SAFETY STUDIES

Because nicotine antibodies may persist in the blood of a vaccinated individuals for months, one of the important questions facing researchers is whether the vaccine would be safe for use in women who are or who may become pregnant.

Pentel presented the results of a study on nicotine transfer to the fetuses of vaccinated rats at the College on Problems of Drug Dependence meeting in Orlando, Fla, in June. His group found that the vaccine behaved in a similar way in mother and fetus. Maternal vaccination did not reduce the total amount of nicotine transferred to the fetus, but some of the maternal antibodies crossed the placenta and bound nicotine in the blood, restricting its distribution to other fetal organs, including the brain.

Within the limits of the rat model, this finding suggests that vaccination should not increase the exposure of the fetus to nicotine, Pentel said. Whether it could instead be protective is speculative. This study was funded by the National Institutes of Health; a study conducted by Pentel's group 5 years prior was funded by Nabi.

Whether these results would apply to humans is yet to be determined because there are important physiological differences between the rat and human placentas. To begin to answer this question, Mahmoud Ahmed, PhD, professor of obstetrics and gynecology at the University of Texas Medical Branch, Galveston, who also presented research at the College on Problems of Drug Dependence meeting in June, is using a model system that uses a full-term human placenta and chambers that simulate the circulation of a mother and fetus. Ahmed's laboratory has previously used the model system to study the effects of other medications, including methadone and other drugs used for the treatment of the pregnant women who are addicted to opioids.

Ahmed and his colleagues found that the nicotine vaccine does decrease the transfer of nicotine across the placenta to the fetus' circulation. Preliminary studies have not revealed any adverse effects on the function of the placenta.

Using vaccines to raise antibodies that target drugs of abuse to prevent addiction in the fetus "is a promising approach," Ahmed said. "But a lot of work still has to be done." □