

Nicotine Vaccine as an Aid for Tobacco Dependence Treatment

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The concept of using a vaccine to immunize against drugs of dependence has been studied over the past three decades. Now these principles are being applied to tobacco. Over the last few years, early stage clinical trials have examined the safety and efficacy of nicotine vaccination for treating tobacco dependence. It is hoped that further studies will show this to be an effective tool in treating this most prevalent addiction.

The principle behind vaccination is that a small amount of a substance (antigen) is injected into a host. The host's immune system will recognize this antigen as foreign, and this will lead to an immune response (i.e. the production of antibodies). Antibodies are specific to certain characteristics on the antigen's surface.

After an initial vaccination, the immune system keeps a memory of the antigen, and if it is introduced in the future, the immune cells are able to produce a large amount of antibodies fairly quickly. These antibodies will bind to the antigens, and allow for other host's defenses to eliminate them.

Since all drugs of dependence exert their influence on the brain, it is important to understand the concept of the blood-brain barrier. There are certain structures as part of the brain's circulation that limit substances entering into the brain. Certain molecules that are too large cannot pass through this "blood-brain barrier" and, therefore, cannot affect brain physiology. In the case of vaccination, this is very important. While the nicotine molecule is small enough to pass freely into the brain, the combined structure of nicotine-antibody is too large to enter, thus, reducing nicotine's effect on the brain. This would, in theory, prevent some of the "kick" that a smoker experiences from the nicotine surge, and could reduce the rewarding effects of smoking, and thus reduce the drive for continued consumption.

In animal studies, the nicotine vaccine has been shown to be effective in reducing the distribution of nicotine to the brain by 65% (Pentel, 2000). Vaccination of rats against nicotine reduces nicotine distribution to the brain even at nicotine doses twice the estimated binding capacity of the antibodies (Satoskar, 2003). This suggests that the vaccine not only sequesters nicotine, but

also directs it away from the brain by some other mechanism. Vaccination of other drugs, such as cocaine, has shown a similar finding that relatively small levels of antibody have a more than expected effect on drug distribution to the brain (Fox, 1996). In animals, antibodies were produced to nicotine even with the continued administration of nicotine to the subject. Therefore, these vaccines could be used even while a subject continues to smoke, and the antibodies would be present when a cessation attempt was made.

There are a few pharmaceutical companies that are working on clinical trials of nicotine vaccine in human subjects. TA-



NIC, a novel nicotine vaccine has been studied in Phase I safety and immunogenicity trials in Belgium by Xenova Research Limited (St. Clair-Robert, 2003). The vaccine is designed to induce nicotine antibodies that would bind free nicotine in the blood. Bound nicotine will not be able to cross the blood-brain barrier. The Phase I trials show that the vaccine is safe and immunogenic using up to six vaccinations during weeks 0-8 and a booster at nine months.

Nabi Biopharmaceuticals has also developed a nicotine vaccination, NicVAX. Phase I trials show safety and antibody response up to 63 days post-vaccination (Lindmayer, 2003). Local reactions were mild to moderate. Single dose vaccine produced antibodies as early as seven days post-vaccination, and these were maintained over four months.

The company has recently announced (August, 2003) initiation of Phase II trials of its vaccine at three study sites testing three dosage levels of the vaccine. A total of 63 patients, divided into three groups, will be

administered up to four doses of the vaccine. Primary endpoints will evaluate nicotine-specific antibody levels, trends in smoking habits during the trial, and safety and tolerability of the vaccine.

The clinical utility for smoking will be that in a vaccinated individual, nicotine will not have the same effect on the brain, and thus smoking may not become as addictive. The implications for current smokers as a tool for cessation, former smokers as a tool for relapse prevention, and never smokers (possibly youth) as a tool for primary prevention, are varied and complex. In addition, this vaccination has potential implications for pregnant women and nicotine's effect on the developing fetus. Obviously, more data and research are required in the years to come. However, this is a novel, interesting, and potentially useful method of treatment for tobacco dependence in the future.

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