Web audio at CurrentPsychiatry.com Drs. Anthenelli and Somoza discuss adherence to TA-CD, and more



# Vaccine for cocaine addiction: A promising new immunotherapy



# Blocking cocaine from reaching the brain may help curb use

nlike opioid or alcohol abuse, for cocaine dependence there are no FDA-approved pharmacotherapies, which leaves psychosocial treatment as the standard of care for the estimated 1.6 million individuals in the United States who abuse cocaine.<sup>1</sup> However, researchers are developing a novel way to help cocaine-dependent patients reduce their drug use. Therapy for addiction-cocaine addiction (TA-CD) is thought to curb cocaine use by engaging the body's immune reaction and stopping cocaine molecules from reaching the brain, thereby reducing the drug's pleasurable effects. One researcher working on this vaccine, Eugene Somoza, MD, PhD-the principal investigator of the Ohio Valley Node of the National Institute on Drug Abuse clinical trials network of 16 universities and treatment programs-discusses with CURRENT PSYCHIATRY Section Editor Robert M. Anthenelli, MD, how TA-CD works and how it might be used in clinical practice.

**DR. ANTHENELLI:** How is immunotherapy being applied to treating cocaine addiction and how does TA-CD work? **DR. SOMOZA:** Our bodies have a very efficient immune system that can recognize foreign proteins and other complex molecules and develop specific antibodies against them that join irreversibly to these molecules to make them inactive. Immunotherapy usually is used to treat disorders that involve very complex molecules. Cocaine is a very simple molecule, but you can attach a simple molecule to a complex molecule and still trigger the immune system. You can use this method to develop antibodies to cocaine. When an individual uses cocaine,

the antibodies will bind to the cocaine in the blood stream and the drug never reaches the brain because the molecule is now too large to pass the blood-brain barrier. The reinforcing properties of addictive agents depend on how fast they get into the brain. By slowing down or even stopping this process, you decrease the pleasurable effect individuals get from cocaine.

The cocaine vaccine that is being tested makes use of the B subunit of the cholera toxin molecule. It is highly immunogenic, and a recombinant of it is available in large quantities.<sup>2</sup> Cocaine molecules are connected to various areas of this complex cholera toxin subunit with covalent bonding. This makes the cocaine a larger target for an antibody response.

The interesting aspect of this process is that the vaccine acts outside of the brain. Other pharmacotherapies being tested, such as modafinil and disulfiram, target receptors or enzymes within the brain, which means that these 2 types of treatment would be synergistic. An early article on cocaine vaccines by Fox et al<sup>3</sup> emphasized that this therapy is compatible with other treatments.

**DR. ANTHENELLI:** After receiving the vaccine, how long does it take for antibody levels to be high enough to produce a therapeutic effect?

DR. SOMOZA: Typically about 8 weeks.

**DR. ANTHENELLI:** Some trials have shown that patients display high variability in antibody levels. Only 38% of subjects in a 24-week, randomized, double-blind, placebo-controlled trial by Martell et al<sup>4</sup> achieved high antibody levels ( $\geq$ 43 µ/mL). Are there ways to predict who will achieve the higher antibody titers and to increase the percentage of people who might develop the antibodies? DR. SOMOZA: Right now there are not. In the Martell study, subjects' antibody response curves-the increase and subsequent decrease in antibody concentration-were very different from individual to individual. We estimate that 40% of patients receiving the vaccine will develop  $\ge 40 \ \mu/$ mL of antibodies; this level is necessary for heavy cocaine users. However, not all patients take large amounts of cocaine, so



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we expect that even if a patient develops  $30 \ \mu/mL$  of antibodies, the amount of cocaine reaching the brain will be reduced although the process may be slower—and using will not be as enticing.<sup>5</sup>

**DR. ANTHENELLI:** How long will the effects of TA-CD last, and how often will patients need to receive booster shots to keep antibody titers high?

**DR. SOMOZA:** The antibodies stay high for approximately 10 to 30 weeks, so you have to give boosters periodically. We need to carefully study if one can give a patient a booster every few months and, if so, how many booster shots would be required.

**DR. ANTHENELLI:** What are the known side effects of the vaccine?

**DR. SOMOZA:** In phase 1 and phase 2 studies, there haven't been any problems at all.<sup>6</sup> Theoretically, we could see some reaction at the injection site such as bruising or red or inflamed skin. In some cases with protein vaccines they've seen systemic reactions like fever. There's also a risk of serum sickness, but this is theoretical based on other protein-based vaccines.<sup>7</sup>

**DR. ANTHENELLI:** Are there any data that address the safety of long-term TA-CD use? **DR. SOMOZA:** We do not have any data on long-term use, but we know what happens over several months. When this project



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# **Clinical Point**

When antibodies bind to cocaine in the blood stream, the molecule becomes too large to cross the bloodbrain barrier



Cocaine vaccine

# **Clinical Point**

We estimate that 40% of patients receiving the vaccine will develop ≥40 µ/mL of antibodies; this level is necessary for heavy users



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# Pharmacotherapy for cocaine dependence: Most evidence is weak

Study	Design	Results
Disulfiram		
Pani et al, 2010 <sup>8</sup>	Meta-analysis of 7 studies with 492 cocaine-dependent patients	Researchers found 'low evidence' supporting disulfiram for treating cocaine dependence
Modafinil		
Dackis et al, 2005 <sup>9</sup>	62 cocaine-dependent patients randomized to modafinil, 400 mg/d, or placebo for 8 weeks	Patients receiving modafinil provided significantly more BE- negative urine samples and were significantly more likely to achieve ≥3 weeks of cocaine abstinence
Anderson et al, 2009 <sup>10</sup>	210 cocaine-dependent patients randomized to modafinil, 200 mg/d or 400 mg/d, or placebo for 12 weeks	Modafinil significantly reduced cocaine craving but did not significantly improve the average weekly percentage of cocaine non-use days
Tiagabine		
Winhusen et al, 2007 <sup>11</sup>	141 cocaine-dependent patients randomized to tiagabine, 20 mg/d, or placebo for 12 weeks	No significant changes in cocaine use vs placebo as measured by self-report and urine BE
Baclofen		
Kahn et al, 2009 <sup>12</sup>	Cocaine-dependent patients randomized to baclofen, 60 mg/d, or placebo for 8 weeks	No significant difference between groups in cocaine use as measured by urine BE
Ondansetron		
Johnson et al, 2006 <sup>13</sup>	63 cocaine-dependent patients randomized to ondansetron, 0.25 mg, 1 mg, or 4 mg twice daily, or placebo for 10 weeks	The odansetron 4 mg group had a significantly greater rate of improvement in percentage of patients with a cocaine-free week compared with the placebo group
BE: benzoylecgonine		

began 12 years ago, investigators worried that if the vaccine prevents cocaine from getting to the brain, cocaine-dependent individuals would just take more and more of the drug and suffer serious consequences. However, in preliminary studies, people have taken as much as 10 times their "normal" amount of cocaine with no adverse events. It looks like the vaccine may ameliorate some of cocaine's effects on the heart. We're certainly not encouraging study subjects to try to override the vaccine blockade, but these preliminary data at least minimize some of those concerns.

**DR. ANTHENELLI:** In clinical trials of TA-CD, during the 8-week ramp-up period where you're waiting for patients' antibody titers to get high enough to have a therapeutic effect, do trial participants receive other treatment?

**DR. SOMOZA:** Participants receive state-ofthe-art cognitive-behavioral therapy (CBT) once a week. We do this to help patients look for triggers to cocaine use and how to handle them, but also to encourage them to stay in the study. It's important that people who enroll in our trials are motivated to stop using. Many patients who have been using cocaine for years haven't been able to own a house, get married, or even buy a car because all of their money is spent on cocaine. Eventually they decide it's not a good idea to keep using forever. These are the participants we'd like to find.

There are other ways of increasing retention, such as rewarding patients for coming to appointments, providing urine for toxicology screens, or getting the boosters. We're hoping contingency management will help keep patients in the trial.

# Next step in addiction vaccines: A human anti-cocaine monoclonal antibody

Promising clinical trials of therapy for addiction–cocaine addiction (TA-CD) and nicotine conjugate vaccines show that immunotherapy may be effective for addictive disorders. However, immune response varies among patients and the vaccines are effective only in those who produce high concentrations of anti-drug antibodies. Our multidisciplinary translational research project has generated a predominantly human sequence monoclonal antibody (mAb) with high affinity (K<sub>d</sub> = 4 nM) for cocaine and specificity over cocaine's inactive metabolites. This mAb (preclinical designation, 2E2) is at an advanced stage of preclinical development for preventing relapse in treatment-seeking cocaine abusers.

Development of 2E2 has met several key safety and efficacy milestones. Because the structure of mAb is mostly human, repeated treatments should be safe and should confer long-term efficacy. 2E2 binds to and sequesters cocaine in the peripheral circulation and dramatically lowers brain cocaine concentrations in mice.<sup>14</sup> Furthermore, 2E2 decreases the effect of cocaine in a rat model of relapse.<sup>15</sup> In FDA-required safety tests, there

### How TA-CD will aid treatment

DR. ANTHENELLI: How do you envision TA-CD could be used in clinical practice? DR. SOMOZA: It could become another tool in our armamentarium for treating cocaine dependence. Currently, there are no FDA-approved medications for cocaine dependence, although some pharmacologic treatments are being studied (Table).8-13 When a patient comes in to be vaccinated, he or she also could receive other treatments if they are available, and the effect potentially would be additive. We would also use CBT because cocaine dependence is a very complex disorder. In CBT patients identify triggers that cause them to want to use and learn how to combat them and make better decisions.

**DR. ANTHENELLI:** Some research shows that TA-CD doesn't stop cocaine use altogether but reduces use. Will that be a deterrent for clinicians who wish to help patients achieve absteinence?

**DR. SOMOZA:** That's true about any medication we develop for addictions. I think

was no apparent cross-reactivity of 2E2 with an extensive panel of human tissues in vitro, indicating that 2E2 likely is safe for patients. The genes encoding the mAb have been cloned and slightly re-engineered to make them even closer to a human sequence and the expressed recombinant protein retains the identical affinity and specificity for cocaine. We continue to work with our industry collaborator, Vybion Inc., to develop a stably transfected mammalian cell line capable of high-level production of 2E2, which is necessary to support in vivo toxicology studies required for an FDA Investigational New Drug application and subsequent clinical trials. This anti-cocaine mAb should be a useful adjunct to TA-CD by supplementing concentrations of vaccine-generated anticocaine antibodies.

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it is magical thinking to say that you can give patients a pill and they will be abstinent for the rest of their lives. If you look at tobacco or alcohol, in practice abstinence is an end point that one has to approximate successively. In addition, permanent abstinence from cocaine is virtually impossible to measure. Because the half-life of benzoylecgonine (BE), the principle metabolite of cocaine, is 6 to 8 hours, this limits the effectiveness of urine toxicology screens in monitoring abstinence. Cocaine-dependent patients might not have used the drug the day before a urine toxicology screen. If a patient says he is abstaining from cocaine, it would be difficult to document it quantitatively without obtaining urine BE levels every day or every other day.

I think clinicians need to get used to the fact that we have to treat cocaine dependence in an incremental manner. A pharmacotherapy that would reduce use and hopefully limit the problems people are having as a result of cocaine use would be a positive step.



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# **Clinical Point**

In addition to CBT, vaccinated patients also could receive other pharmacologic treatments



Cocaine vaccine

### **Clinical Point**

TA-CD may be available to clinicians in 7 to 10 years if it is found to be effective



Visit this article at CurrentPsychiatry.com for additional information about TA-CD



# Vaccines for nicotine: Another tool to help patients break the habit

Dependence on nicotine—the main addictive agent in cigarette smoke and other tobacco products—also is being targeted with vaccines. Like cocaine, the nicotine molecule is too small to provoke an immune response by itself. Therefore, nicotine derivatives linked to virus-like particles<sup>16</sup> or detoxified bacteria-derived proteins<sup>17</sup> are immunogenic enough to stimulate an antibody response. With once-monthly vaccinations of these conjugated nicotine compounds, patients can produce sufficient antibodies to sequester nicotine in the peripheral bloodstream before it crosses the blood-brain barrier to produce its rewarding effects. Animal and human studies have found proof that this concept may work. These immunotherapies do not seem to provoke acute nicotine withdrawal and patients do not increase their smoking rates to try to counteract the antibodies' nicotine-scavenging effects.<sup>16-19</sup> As was the case with the cocaine trial,<sup>4</sup> smoking cessation efficacy is positively correlated with the individual's antibody titer response. Published phase I and II trials indicate that these vaccines may be safe and well-tolerated; mild reactions at the intramuscular injection site are the most commonly reported adverse event.<sup>16-18</sup> Larger phase III clinical trials are underway.<sup>20</sup> **Robert M. Anthenelli, MD** 

**DR. ANTHENELLI:** If TA-CD is found to be effective, what is the earliest it might come into clinical use?

**DR. SOMOZA:** I would speculate that it would be 7 to 10 years.

**DR. ANTHENELLI:** What other kinds of research are going on as far as vaccines for cocaine? **DR. SOMOZA:** There is a strain of transgenic mice that when stimulated produce human, as well as mice, antibodies. At the University of Cincinnati, Andrew Norman, PhD, was able to immunize these mice and they generated human antibodies against cocaine (*Box 1, page 19*).<sup>14,15</sup> Then you'll have vials of monoclonal antibodies that you can administer to your patient. However, this is still in early testing.

**DR. ANTHENELLI:** We've talked about immunotherapy and how it might work for the treatment of cocaine addiction. How might these types of vaccines be used for treating other substances of abuse?

**DR. SOMOZA:** Investigators are currently working on a vaccine for nicotine dependence

# **Bottom Line**

(*Box 2*)<sup>4,16-20</sup> and there's a vaccine being developed for methamphetamine,<sup>21</sup> but it is not as advanced as cocaine. A similar methodology has been used for some time to treat digitalis overdose. There is no antidote for digitalis toxicity, so researchers have developed an antibody—digoxin immune fab—that attaches to the drug, which is then excreted through the kidneys. I fully expect that this methodology eventually will work for cocaine, methamphetamine, and nicotine dependence. My hunch is that producing human antibody in industrial quantities would be the most sensible way to eventually make this work.

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Immunotherapy for cocaine dependence could prevent cocaine from crossing the blood-brain barrier, making the drug less pleasurable. The vaccine would work synergistically with other treatments for substance abuse. More research is needed to boost the amount of antibodies in the blood stream, which means that the vaccine is years from clinical use.

### **Related Resource**

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#### Drug Brand Names

Baclofen • Lioresal Digoxin • Lanoxin Digoxin immune fab • Digibind Disulfiram • Antabuse Modafinil • Provigil Ondansetron • Zofran Tiagabine • Gabitril

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## Online only box



Cocaine vaccine



## Additional commentary from Drs. Anthenelli and Somoza

#### **Treatment adherence**

**DR. ANTHENELLI:** We know from working in the addiction field that compliance with medication regimens is a big challenge. What are the data regarding adherence to TA-CD?

**DR. SOMOZA:** We don't have any specific data about adherence to the vaccine, but it is probably similar to any other medication for addiction. Remember that cocaine-dependent patients often are erratic and don't use planners to set up their day. If you look at clinical trials over the past 20 years, if you get 75% retention you're doing really good, but quite often you see 50% or 25% retention. With TA-CD, retention is going to be worse because you have to wait 8 weeks before patients build up enough antibodies to have therapeutic effect. I'm hoping we can convince the FDA to look at the relationship between antibody generation and improvement in treatment efficacy. Obviously if patients don't develop antibodies they're not going to get better.

### Patient characteristics

**DR. ANTHENELLI:** I know it's a little early, but if you had to use your crystal ball,

what type of patient do you think that TA-CD might work best for?

**DR. SOMOZA:** Certainly it would be for people that are motivated to stop using. If they really don't want to stop using cocaine, probably nothing will work. These patients could get the vaccine and boosters and it won't do them any good. They'll take it and nothing happens.

#### Future research

DR. ANTHENELLI: One of the things you have discussed is who will achieve enough antibody titers to make TA-CD effective. Are there other kinds of research you think will be related to this? DR. SOMOZA: Increasing the serum concentration of the antibodies is one. Another would be to increase the fraction of people who develop high levels of antibodies. One wonders if we could use a different protein that would increase the immunogenicity of the vaccine. If we use 2 different proteins, perhaps the effects would be additive. In an early study of mice, Fox and colleagues<sup>a</sup> used a blood protein, not a cholera toxin.

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