

# Immune to addiction: the ethical dimensions of vaccines against substance abuse

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**Promising advances have been made in recent years for a unique class of immunotherapies that use vaccination to combat substance-use disorders. Although such vaccines are potentially useful for addictions, they raise a variety of ethical and social questions.**

The appearance of anti-addiction immunoprophylaxis represents a paradigm shift both in vaccinology, which has been traditionally focused on infectious, somatic disease, and in addiction medicine, which traditionally has aimed to rehabilitate patients through a combination of cognitive and behavioral therapies, pharmacological treatments and maintenance programs. Interest has increased in the development of vaccines for the prophylaxis and treatment of many substance-use disorders. Vaccines to treat addiction to nicotine, methamphetamine and morphine, or phencyclidine are at various stages of preclinical or clinical investigation<sup>1</sup>. The ethical questions raised by the development and deployment of such vaccines are multifaceted and are pertinent to patients, clinicians, researchers and society (Box 1). As it is furthest along in trials and more is understood about its biology, the emerging vaccine used as therapy for addiction—cocaine dependence (TA-CD) is the focus here as a paradigm case that elucidates many of the questions raised by other proposed immunological

interventions for substance abuse. Key issues posed by the availability of vaccines of this kind include their prophylactic use, therapeutic use and unintended socioeconomic consequences and the ethics of conducting research to bring such vaccines to market.

## Why vaccinate for substance dependence?

The growing interest in vaccines of this kind has been motivated by the considerable effects of substance-use disorders on health and society and by the inadequacy of many existing treatments. Such issues are particularly notable in the epidemiology of cocaine use and dependence. According to the US Department of Justice, in 2008, approximately 5.3 million people 12 years of age or older reported cocaine use in the past year. Cocaine accounts for a larger percentage of visits to the emergency department than does any other illicit drug<sup>2</sup>. In addition to its own risks, cocaine is often surreptitiously 'cut' with other unsafe substances before sale, which adds to the drug's threats to health. Cocaine use also adversely affects rates of crime and productivity at work. Despite the severity of this public-health problem, there is no medication approved by the US Food and Drug Administration for the treatment of cocaine dependence. Some products are being studied and used 'off-label' for this purpose with limited success<sup>3</sup>. The disproportionately high relapse rates of patients treated with existing psychopharmacotherapies, coupled with the growing socioeconomic burdens of cocaine dependence<sup>4</sup>, have triggered recent interest in the exploration of new kinds of treatments.

The TA-CD vaccine, which is now entering phase II multisite clinical trials, is produced by

the conjugation of a cocaine derivative (succinylnorcocaine) with an inactive cholera toxin as an adjuvant (Box 2). This immunogenic duo elicits cocaine-specific antibodies that bind to cocaine after intake, which prevents the drug from crossing into the central nervous system and blunts its psychoactive effects<sup>5</sup>.

Unlike anti-cocaine pharmacotherapies, which act in the brain to modulate the effects of cocaine or mitigate withdrawal symptoms, the active cocaine vaccine triggers the production of antibodies that sequester cocaine in the blood to prevent it from reaching the brain<sup>5,6</sup>. TA-CD has the dual potential of treating and preventing cocaine dependence by recruiting the immune system to block cocaine from crossing the blood-brain barrier<sup>5-7</sup>. Other emerging vaccines for the treatment of addiction, including those that target addiction to nicotine and opiates, typically operate through analogous immunological mechanisms and have similar theoretical potential<sup>1</sup>.

## To treat or prevent?

Clinical testing of the TA-CD vaccine has demonstrated its therapeutic promise. In early trials, the vaccine was well tolerated and demonstrated a dose-dependent potential to decrease likelihood of drug use in human and animal subjects<sup>5,6</sup>. Should research outcomes remain favorable for this product or others like it, the potential use of a vaccine of this kind would raise many ethical and social concerns that would require attention and deliberation. Chief among such questions is whether such a vaccine ought to be used to treat only those already diagnosed with dependence or whether it should also be used to prevent dependence in healthy people.

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**Box 1 Ethical questions in substance abuse vaccine development and implementation****Medicine & Public Health**

- Should vaccines be used to control risky or destructive behaviors?
- Ought vaccines be used only to treat or also to prevent drug dependence?
- Is drug dependence sufficiently comparable to infectious disease to warrant similar public health policies?
- Who should be vaccinated?
- Which agencies or professionals should administer vaccines against substance abuse?
- Should vaccination be compulsory or optional?
- Is there a professional obligation to protect children from future addictions?
- How can clinical equipoise be maximized in trials?

**Society**

- Would mandated vaccination trigger replacement-drug markets?
- Will the emergence of substance abuse vaccines lead to a lower perceived risk of substance use?
- What strategies should be implemented to address the social determinants of substance abuse?
- How can equitable access to the vaccine be maximized?
- Do the costs of the development and implementation of vaccines against substance abuse outweigh the benefits?

**Individual people**

- Will high-risk people become the subject of more stigma?
- How might the use of vaccines for substance abuse affect a person's sense of personal responsibility in recovery?
- Would the prophylactic use of a vaccine against substance abuse undermine the right to future choices or options?
- Does the use of a vaccine against substance abuse undermine the ability to exercise what might be considered commendable self-restraint?
- How can therapeutic misconceptions be addressed?
- Because drug cravings outlast successful vaccination, to what extent should complementary strategies be used to treat drug cravings?
- Is immunity to addiction an enhancement or a treatment?

If a vaccine against cocaine addiction is shown to be safe and highly effective, proposals to include it among the vaccinations routinely administered or even mandated for certain populations are likely to attract considerable interest. For vaccines now licensed, such mandates exist for children in public schools or daycare facilities, college students, members of the military, healthcare professionals, immigrants and other groups. In the specific case of a vaccine against cocaine, mandates directed at specific populations, such as those eligible for parole or those who accept welfare, have already been suggested<sup>8</sup>. People on trial for drug-related offenses would also be a likely population for such a policy, which would create another potentially attractive alternative to incarceration. Exploring attitudes toward such proposals would probably illuminate underlying assumptions about the nature of addiction and the place of its treatment and prevention in the traditional parameters of public health.

The complexity of the choices that would be presented by this novel type of vaccine is underscored by the fact that it is aimed at controlling behavior that is often deemed ethically fraught. Thus, the more fundamental question of whether such vaccines ought to be used prophylactically revolves around two distinct concerns: first, the ontology of substance

dependence; and second, the parameters of free will and autonomy.

**Is addiction 'infectious'?**

Determining the appropriate use of such a vaccine demands clear understanding of the nature and nosology of substance dependence. How substance dependence is characterized and classified informs the appropriateness of strategies aimed to prevent or treat it. In recent years there has been a marked departure away from the traditional understanding of substance dependence, in which it is framed as a failure of self-control that can lead to addiction, to one in which it is framed as a multivariate neurobiological disease with genetic, anatomical, chemical and physiological determinants<sup>9,10</sup>. Researchers are beginning to identify a heritable profile of brain abnormalities that may predispose individual people and family members to addiction<sup>9</sup>.

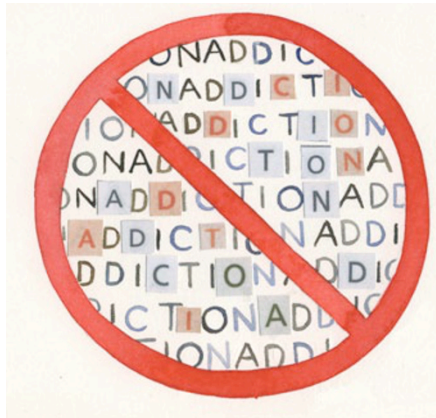
Whereas traditional models of substance dependence place the burden of recovery squarely on the patient and his or her ability to exert self-control, present models emphasize the need for medical interventions that treat addiction as a neurobiological disease<sup>9</sup>. Thus, some analysts find it appropriate to make drug dependence the focus of a large-scale preventative public-health strategy that includes mandated vaccination. For example, some pro-

ponents of this position have even advocated incorporating vaccines against addiction into compulsory state-mandated statutes for the immunization of 11- and 12-year-old school-children<sup>11</sup>.

The preemptive compulsory use of this sort of vaccine would be unprecedented, because the condition it aims to prevent is not infectious and the vaccine does not confer herd immunity<sup>12</sup>. In addition to the prevention of disease transmission, the benefit of herd immunity is, historically, a persuasive component of any justification for vaccination mandates.

However, a case can be made for 'herd' immunity for this type of vaccine. Although substance dependence is not itself an infectious disease, research has shown that cocaine dependence, for example, places a person at high risk of contracting infectious diseases, including tuberculosis and AIDS<sup>13</sup>. Moreover, social-contagion theorists have shown that one person's behavior is very likely to influence the behavior of others, which suggests a more 'infectious' disease model for addictive behavior<sup>14</sup>.

It may be appropriate to manage the prevention of addiction akin to the prevention of infectious disease, given such emerging knowledge of risk factors and social contagion. As resistance to the present vaccine mandates illustrates, any eventual policy may require



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Vaccines against substance abuse raise many ethical and social questions.

'opt-out' options and exemptions. Greater attention to when, why and for whom such exemptions may be warranted is needed as part of public-health policy, both for vaccines against infectious disease as well as for potential vaccines against addiction.

### Parameters of autonomy

The ethical principle of respect for autonomy emphasizes that a patient's capacity for self-determination ought to be respected and that patients should be free from coercion. This principle invites the dilemma of whether such vaccines might in some way do harm by minimizing the extent to which people can make autonomous choices about drug use. However, in dealing with addicted patients, the parameters of this principle can be ambiguous, especially if temporary restrictions on a patient's autonomy could create more autonomy in the long term<sup>15</sup>. The extent to which respect ought to be accorded to a patient's choices is particularly unclear when the drug-seeking behavior of an addicted patient is considered biologically coerced<sup>10</sup>, akratic (a weakness of will) or compulsive<sup>16</sup>.

The fundamental question motivating this debate is whether an addict is truly autonomous. This uncertainty gives rise to the associated issue of whether the principle of respect for autonomy extends to preferences that are the result of addiction. The principle of respect for autonomy may correspondingly suggest that people have the right to exercise the choice not to be addicted, rather than being made biologically immune to this possibility. The concern is that there is some virtue in the choice not to become addicted. For example, people vaccinated against a harmful drug such as cocaine would be deprived of the chance to show commendable self-restraint if they were simply 'immune' to ever feeling the psychoactive effects of cocaine<sup>17</sup>.

A likely argument against the preventative, compulsory use of such a vaccine in healthy people is that such a mandate would inappropriately violate a person's liberty to make 'victimless' or autonomous choices about drug use. However, given the present understanding of addiction and peer-to-peer influence, it is arguable that cocaine use is not victimless and is in a sense 'contagious'<sup>9,10,14</sup>. This prompts the question of why, given the biomedical model of addiction and identifiable risk factors, preventative strategies should be deemed inappropriate.

### Who should be vaccinated?

The question of how a preventive vaccine of this kind ought to be used must be considered in tandem with the question of who ought to be vaccinated. In the case of the vaccine against cocaine, some parents may argue that it is their moral obligation to protect their children from developing cocaine dependence. Some might argue that targeting at-risk groups or people would be stigmatizing. Another likely opposing view would suggest that the vaccination of children or high-risk people against addiction constricts their rights to future choices and options<sup>18</sup>, a future in which they ought to be able to experience the effects of cocaine if they so please.

The issue of allowing a person to choose to use addictive substances such as cocaine or restricting that possibility carries striking parallels to genetic enhancement. This area has prompted similar debates over biomedical interventions that aim for some phenotypic ideal, behavioral or otherwise<sup>19</sup>. Such issues bring to light underlying problems that surround how the concept of health should be considered and how this understanding ought to guide medical decision-making. It also requires assessment of whether immunity to addiction should be considered an enhancement or a treatment.

The preemptive use of vaccines against addiction raises the further concern that those who are vaccinated will be stigmatized as 'high-risk pariahs'<sup>20</sup>. The issue of stigmatization has figured prominently in ethical considerations pertaining to the use of potential vaccines against human immunodeficiency virus. It has also affected willingness to participate in clinical trials and to volunteer for vaccination<sup>21</sup>. It will be imperative to consider preemptively these unwanted outcomes, as well as strategies to attenuate them, in the construction of future research and in the use of the vaccine against cocaine and others like it.

Although it is probable that a vaccine against cocaine would be used to aid only those with preexisting dependence, at least initially researchers have suggested that the vaccine could be administered to cocaine-dependent pregnant women to protect fetuses or neonates from the effects of cocaine abuse<sup>22</sup>. Others have discussed incorporating this vaccine into parole programs for those incarcerated for cocaine use-related infractions<sup>17</sup>. Requiring or providing incentives for vaccine administration in each of those scenarios would introduce a range of ethical complexities that highlight the difficulties inherent in making policies on the proper use and distribution of such a vaccine. Forcing treatment on either pregnant women or parolees would raise ethical concerns that offering the choice of treatment does not.

### Safety and therapeutic misconceptions

Issues of safety and therapeutic misconceptions further complicate the ethics of vaccines against addiction. Clinical trials of the TA-CD vaccine have brought these issues into focus. Unlike many of the pharmacotherapies now being studied for the treatment of cocaine dependence, the leading candidate vaccine against cocaine does not attenuate cravings or the symptoms of withdrawal. Thus, users might attempt to use excessively high quan-

## Box 2 The TA-CD vaccine

<b>Vaccine vector</b>	• Conjugate of cocaine derivative and recombinant cholera toxin B
<b>Effector mechanism</b>	• Cocaine-specific immunoglobulin G
<b>Proof of concept</b>	• Antibodies elicited through vaccination limited cocaine from reaching the brain by up to 80% in rats <sup>7</sup>
<b>Early clinical trials</b>	<ul style="list-style-type: none"> <li>• 38% of users achieved sufficient serum antibody levels after vaccination to diminish cocaine use<sup>6</sup>; the cocaine-blockade in these users remained active for up to 2 months</li> <li>• Booster vaccinations are needed to maintain sufficient serum concentrations of antibody<sup>5,6</sup></li> <li>• No adverse physiological effects on the brain have been observed</li> </ul>

tities of cocaine to overwhelm the vaccine's effects<sup>5</sup>.

Patients associating the efficacy and function of this vaccine with that of other vaccines they have previously received may believe that after they are vaccinated, their cocaine dependency will simply 'dissolve'. Instead, the present formulation of the vaccine does not confer sufficiently high serum concentrations of antibody until 2 weeks into treatment. It also requires regular readministration to maintain functional concentrations of antibody<sup>6</sup>. The need for frequent booster vaccinations diminishes the treatment's cost-effectiveness and makes prophylactic use of the present version of the vaccine unlikely. Furthermore, there is considerable variability among individual immune responses to the vaccine<sup>5,6</sup>. Some vaccinated cocaine users never produce concentrations of antibody adequate to substantially forestall the effects of cocaine. As the desire to use the targeted substance endures, many will continue to attempt to use the substance at higher and higher doses or, in the case of polydrug users, begin to rely more heavily on other substances<sup>23</sup>.

### Unintended socioeconomic consequences

The possible socioeconomic consequences of a vaccine such as the TA-CD vaccine add to the complexities that face its introduction and use. It is plausible that widespread prophylactic use of this vaccine could trigger a replacement drug market, such that addiction-prone people would simply turn to other substances if the option to use their substance of choice were eliminated through vaccination. As has been observed in trials of vaccines against human immunodeficiency virus, there might be a decrease in the perceived risk of, or an increased interest in, an unsafe behavior if a vaccine tailored to it were to become available, which would thereby increase the likelihood that people would try it<sup>21</sup>. Providing a quick method for the cessation of substance abuse might remove a major deterrent; that is, the possibility of developing an enduring addiction<sup>12</sup>.

Although a vaccine such as the TA-CD vaccine may effectively address the biological determinants of addiction, it does not address the more pertinent social and environmental determinants of addiction. According to one study, substance use and abuse "may partly reflect biological differences, but it is more likely

that they can be explained largely by socioeconomic differences, cultural factors, and prejudice and discrimination, both institutional and individual."<sup>24</sup> If a potential 'blockbuster' vaccine for a substance-use disorder is released, the causal role of these social factors may come to be overlooked and left unaddressed. Moreover, those who do not choose to be vaccinated or to have their children vaccinated could find themselves the objects of even greater social stigma should they later become addicted<sup>25</sup>. The connotations of the term 'vaccine' itself introduce the potential for widespread misconceptions about what the intervention is meant to do and the nature of the addiction. This underscores the importance of ensuring that the public is well informed about the limitations of such a vaccine.

### Conclusions

A vaccine against cocaine addiction presents many social, legal and ethical issues. These issues are emblematic of those linked to the development and deployment of other vaccines that belong to the evolving category of immunotherapies that target substance-use disorders. A vaccine will not eliminate the need for other interventions. Complementary therapeutic measures, such as cognitive-behavioral therapy or maintenance programs, would still be needed to attenuate the cravings and drug-seeking habits associated with substance dependence. Social programs need to be carefully crafted to address the underlying socioeconomic determinants of drug use and addiction.

In investigating such vaccines, researchers must consider the principle of clinical equipoise, designing equitable and sensitive clinical studies that diminish undesirable outcomes through careful implementation, multilevel monitoring and continuous evaluation. Any anti-addiction vaccination strategy should be coupled with a comprehensive educational scheme to minimize therapeutic misconception and to maximize adherence to treatment schedules.

The temptation to use a potential vaccine to 'solve' the immense problem of abuse and addiction is enormous, but the ethical challenges that would accompany any proposal for widespread or mandatory use are daunting. The opprobrium and suspicion that vaccines often seem to attract portends intensified controversy when the targets are behavioral phenotypes. It

is vital to address these issues now, lest some of the battles, misperceptions and fear-mongering that have dominated vaccine policy too much resurface in the ethically fraught area of addiction treatment.

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