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Ethical and policy issues in using vaccines to treat and prevent cocaine and nicotine dependence

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Abstract

Purpose of review: To describe the rationale of vaccines against cocaine and nicotine, to review progress in developing and trialing vaccines to treat dependence on these drugs and to discuss some of the ethical issues that may arise from their use in legally coerced addiction treatment or for prevention of addiction in adolescents.

Recent findings: Several randomized controlled trials of cocaine and nicotine vaccines for relapse prevention have produced mixed results. The studies demonstrate that it is possible to raise antibodies to cocaine and nicotine in humans. In abstinent patients who show high levels of drug antibodies, the rewarding effects of these drugs are attenuated. Phase 2 trials have not found nicotine vaccines to be superior to placebo because only a third of those vaccinated develop sufficient levels of antibody to block the effects of nicotine.

Summary: Vaccines are a novel approach to relapse prevention that need to more reliably induce immunity in a larger proportion of vaccinated patients if they are to protect against relapse after achieving abstinence. Vaccines are unlikely to prevent addiction in adolescents. Their use under legal coercion should only be considered after considerable experience with their use in voluntary patients.

Introduction

'Drug vaccines' are a novel approach that primarily aim to reduce relapse to addiction after abstinence has been achieved. They induce the immune system to produce antibodies that bind to the molecules of drugs of dependence (e.g. cocaine or nicotine) and prevent them from producing their rewarding effects in the brain [1–3,4••,5•]. Antibodies that are produced by exposing the immune system to a protein molecule combined with the drug molecule bond with the drug in the bloodstream to form a large molecule that is unable to cross the blood–brain barrier and act on dopamine receptor sites in the brain's 'reward centres' [4••].

Experimental proof of a drug vaccine was provided in 1974 when morphine antibodies were shown to reduce heroin self-administration in rhesus monkeys [6]. A heroin vaccine was not developed because of the widespread use of oral methadone and the development of naltrexone to block the effects of heroin [1]. Vaccines have since been developed for nicotine, cocaine, phencyclidine and methamphetamine [1], but most research has been on cocaine and nicotine vaccines, which are the focus of our review.

In rat models of addiction, antibodies induced to cocaine [7–10] and nicotine [11,12] substantially reduce the amount of these drugs that reaches the brain [13]. Immunization against cocaine and nicotine attenuates self-administration [7] and suppresses dopamine release in the nucleus accumbens shell [13].

Why develop human vaccines for nicotine and cocaine?

Tobacco smoking is a major cause of global disease burden [14]. Pharmacological treatments to assist smokers to quit, such as nicotine replacement therapy (NRT), bupropion and varenicline, are only modestly more effective than unaided quitting [15–17]. More effective drug interventions are needed to increase smoking cessation rates.

Cocaine is one of the most widely used illicit drugs in the world [18]. Heavy cocaine users develop anxiety and affective disorders [19] and paranoid psychoses [20]. They are also at increased risk of cardiac arrhythmias and strokes [21] and HIV infection via risky sexual behaviour and sharing injection equipment [22].

There are no effective pharmacological treatments for cocaine dependence [23]. Psychosocial treatments reduce cocaine use, but there are substantial rates of treatment drop out and relapse to cocaine use [24,25]. More effective drug treatments for cocaine dependence are needed [26].

Use of drug vaccines to prevent relapse

The major intended use of vaccines against nicotine or cocaine is to prevent relapse after dependent users of these drugs have achieved abstinence. The hope is that antibodies will attenuate the rewarding effects of these drugs in the first few months after cessation when users are most likely to relapse. Ex-users would be given a series of vaccinations in combination with behavioural programs to reduce the chances that a 'slip' to drug use would lead to a return to daily cigarette smoking or regular cocaine use [27].

A nicotine vaccine has three potential advantages over NRT, bupropion and varenicline as a cessation aid: it could be administered on five to six occasions and produce effects that lasted for several months, thereby improving compliance and treatment outcome [28,29]; it may have fewer adverse effects because antibodies do not act on the central nervous system (CNS) as bupropion and varenicline do [28]; and it could be used in combination with bupropion or varenicline to reduce craving after cessation [27,29,30] and with psychosocial interventions to support the maintenance of abstinence.

A cocaine vaccine could have similar advantages, that is, it would not require daily dosing; it could be used in combination with anticraving drugs; and it would probably have fewer adverse side-effects, reducing the high rates of discontinuation seen in the use of other drugs to treat cocaine dependence [26].

Both types of drug vaccine also have some limitations. Animal studies indicate that the blockade of both nicotine and cocaine vaccines can be surmounted by increasing the dose of the drug. This looks most likely to occur when cocaine is injected or smoked, because the rapid absorption of the drug may not allow sufficient time for antibodies to bind to all of the cocaine before it reaches the brain [31,32]. A cocaine vaccine could also be circumvented by using other drugs with similar stimulant effects, such as methamphetamine [31]. Nicotine vaccines could be circumvented by smoking more cigarettes in rapid succession or by smoking while wearing a nicotine patch.

Human trials of drug vaccines

Kosten et al. [33] reported a phase 1 trial of a cocaine vaccine (TA-CD) in 34 abstinent cocaine abusers in a residential treatment program. Twenty-seven received three increasing doses of the vaccine at monthly intervals and 24 were followed up for 3 months and 15 at 12 months after vaccination. The vaccine produced only mild, short-lived adverse reactions at the site of injection. It

induced antibodies to cocaine after the second vaccination, the level of which was maintained up to 2 months after the third vaccination. Levels then fell rapidly to baseline by the end of a year.

Martell et al. [31] assessed the vaccine in an open-label 14-week study in 16 cocaine-dependent participants. The first four participants received 400 μg in four doses of 100 μg each over 4 weeks. The remaining 12 received 2000 μg in five vaccinations of 400 μg. Cocaine use was assessed by thrice-weekly supervised urine tests and treatment outcome was assessed 6 months after vaccination. The vaccine was well tolerated and induced variable immunogenicity. Overall there was no difference between vaccines and placebo, but those who received the higher dose of vaccine had fewer cocaine-positive urines and took longer to relapse to cocaine use than those receiving lower doses. All vaccinated participants who used cocaine reported that its euphoric effects were attenuated for up to 6 months after immunization.

Box. 1

Key points

- Vaccines against cocaine and nicotine are a potentially useful way of preventing relapse in smokers and dependent cocaine users after quitting.
- Vaccines sequester drugs in the bloodstream, preventing them from entering the brain; they may have fewer side-effects than drugs that act on the central nervous system; and they may have better rates of patient compliance than oral drugs.
- Clinical trials demonstrate that antibodies attenuate the effects of cocaine and nicotine for several months after vaccination in the third of patients who achieve therapeutic levels.
- The major clinical challenge is to reliably produce therapeutic levels.
- The major clinical challenge is to reliably produce therapeutic antibody levels in a larger proportion of vaccinated patients.
- The use of vaccines under legal coercion or compulsion and their preventive use in adolescents need to be approached with great caution

Martell et al. [34] reported a phase 2 randomized double-blind controlled trial of the vaccine in 94 regular crack cocaine users who were enrolled in methadone maintenance treatment. Participants received five doses of either placebo or the cocaine vaccine over 12 weeks. The researchers monitored cocaine use using urine tests during weeks 8–12 and 24 after vaccination. Only 21 (38%) of those vaccinated achieved antibody levels likely to attenuate the effects of cocaine. These participants had fewer cocaine-positive urines than vaccinated participants who did not achieve these antibody levels and those who received the placebo. More of the successfully vaccinated participants achieved a 50% reduction in cocaine use than those on placebo (53 vs. 23%). The vaccine only provided 2 months of adequate antibody protection. A second phase 2 clinical trial of the TA-CD vaccine commenced in 2010 [35].

There are three nicotine vaccines undergoing human trials [28]. Each uses a unique antigenic molecular approach (see [36] for details). All vaccines have undergone phase 1 and phase 2 trials, but results have only been reported for two of these (see Table 1). The NicVAX vaccine is the closest to reaching the market after receiving fast track designation by the US Food and Drug Administration in 2006 and a $10 million grant from the National Institute on Drug Abuse for phase 3 clinical trials [37].

Table 1 Results of phase 2 trials of nicotine vaccines

Immune response	Percentage of vaccinated smokers (%)	Percentage abstinent 6 months (%)	RR 6 months	Percentage abstinent 12 months (%)	RR 12 months
NIC002[a,b]					
High	33.3	56.6	1.8 (0.9–3.7)	41.5	2.0 (0.9–4.2)
Low/medium	66.6	32.1	1.0 (0.5–1.9)	23.6	1.1 (0.6–2.2)
Placebo	–	31.3	1.0	21.3	1.0
NicVAX[c,d]					
High	30	24.6	2.0 (0.9–4.7)	18.0	3.0 (1.0–8.6)
Low/medium	70	10.0	0.8 (0.4–1.9)	2.9	0.5 (0.1–1.7)
Placebo	–	12.0	1.00	6.0	1.0

RR, relative risk.
[a] For 6 months, abstinent weeks 8–24.
[b] For 12 months, abstinent weeks 8–52.
[c] For 6 months, abstinent weeks 19–26.
[d] For 12 months, abstinent weeks 19–52.

The Cytos AG NIC002 vaccine was evaluated in a placebo-controlled trial of 341 smokers: two-thirds received the vaccine and one-third received placebo. The active vaccination comprised five injections of 100 μg once a month. Outcome was continuous abstinence during weeks 8–24 and 8–52. After participants who also used NRT were dropped, outcome data were available on 239 patients who were divided (on levels of nicotine antibodies) into low, medium and high responders. There was no difference in abstinence rates among the low and medium responders and placebo groups. Those in the top third of responders had higher abstinence rates at the 6 and 12-month follow-ups (see Table 1) [38]. A second phase 2 trial was completed in 2009 [39], but results have not yet been reported.

Nabi Biopharmaceuticals reported a phase 2 trial of NicVAX in 301 smokers who received varying doses over 6 months. The doses ranged from 200 μg in four doses to 400 μg in five doses [40]. Abstinence was assessed for weeks 19–26 and 19–52 after vaccination. The 30% of participants who developed the highest level of nicotine antibodies (61 of 201) had higher abstinence rates at both follow-ups than those on placebo. In the remaining 70% of vaccinated participants, abstinence rates were no better than placebo (Table 1). At 12 months, the abstinence rates were 16% in the 400 μg group, 14% in the 200 μg group and 6% in the placebo group. Two phase 3 trials of NicVAX with a six-dose schedule commenced in 2009 and 2010 [41,42].

Celtic Pharma completed a phase 2 trial for TA-NIC in February 2009, but no results have been released [43].

Challenges in delivering clinically effective drug vaccines

The mixed results of the small number of small-scale controlled trials of cocaine and nicotine vaccines suggest that a number of major technical challenges need to be overcome before vaccines are approved for clinical use.

Clinical trials have so far reported modest efficacy. The abstinence rates among those vaccinated against nicotine have been no better than placebo, but rates have been superior to placebo in the third who achieved therapeutic antibody levels. Increasing the number of doses and/or the size of the dose may improve immunogenicity [37,44]. This may also increase adverse effects so that the safety and efficacy of the revised dosage schedules will need to be established.

It takes up to a month for the vaccines to achieve a therapeutic immune response, during which time patients will be vulnerable to relapse. Monoclonal antibodies could provide passive immunity during this time, but such antibodies are expensive and can produce adverse side-effects [45].

Nicotine vaccines will need to be shown to be more effective than NRT, bupropion and varenicline and any new cessation aids. They will also need pharmaceutical company funding for trialing and clinical approval.

If effective drug vaccines are approved for therapeutic use, patient access will depend upon their cost and the preparedness of patients and third parties (e.g. governments and health insurers) to pay the cost. The healthcare system will need to ensure that poorer patients are not denied access, because both cocaine use and cigarette smoking are concentrated in lower socioeconomic groups [46].

Using a cocaine vaccine under legal coercion

Drug treatment under legal coercion is treatment provided as an alternative to imprisonment to persons who have been charged with or convicted of an offence to which their drug dependence has contributed [47]. Treatment is provided under the threat of imprisonment if the person fails to comply. Its main justification is that treating offenders' drug dependence will reduce their chance of reoffending [47,48].

A reasonable case can be made that coerced addiction treatment is legally and ethically justified if the rights of the individuals were protected by 'due process'; if effective and humane treatment is provided [49]; and offenders are allowed two 'constrained choices': first, whether to participate in drug treatment or be dealt with by the criminal justice system in the same way as anyone charged with their offence and, second, if they agree to treatment, a choice of the type of treatment [47].

On this analysis, it would be ethically defensible to include a cocaine vaccine among the treatment options from which offenders could choose. It would be more controversial to compel its use. If a cocaine vaccine were used under legal coercion, its safety, effectiveness and cost-effectiveness would still need to be rigorously evaluated because patients may attempt to overcome the immune blockade by increasing their cocaine dose or using other drugs [50]. Any such use should be implemented cautiously and only after considerable experience has accumulated in using it to treat voluntary patients [50].

Preventive use of drug vaccines

The term 'vaccine' may raise parental expectations that vaccines can be used to prevent nicotine or cocaine dependence in their children [45,50,51]. The preventive use of drug vaccines will be ethically contentious. Children would be vaccinated at the request of their parents because, as minors, they are not legally able to consent. As parents already make choices on behalf of their children that affect their lives as adults (e.g. regarding their diet and education), some have argued that immunization against nicotine or cocaine is a decision that parents have the right to make [51,52]. This is likely to be contested.

The preventive use of a vaccine in healthy young people will require stronger evidence of safety and efficacy than shorter-term use to reduce relapse in adults who are nicotine or cocaine-dependent. Obtaining evidence to meet regulatory requirements for such use is likely to be very expensive [45,50] and pharmaceutical companies may be reluctant to seek such approval. Community concerns about the safety of vaccinations against infectious diseases may also deter investment in preventive studies of drug vaccines [50].

There are also practical impediments to the preventive use of drug vaccines. The limited period of protection provided by the current vaccines will require frequent booster injections throughout adolescence. Alternatively, a longer-acting vaccine will need to be developed. The costs of universal vaccination in adolescence, and the likely modest ability to prevent drug dependence, make it unlikely that there would be public funding for the universal preventive vaccination against drugs of dependence. Also, because the vaccine can be circumvented by using larger doses of drugs,

vaccination could potentially have counterproductive effects if adolescents tested its efficacy by smoking cigarettes or using cocaine [50].

Conclusion

Animal studies suggest that drug vaccines are a biologically plausible immunotherapeutic intervention that could potentially be useful in preventing relapse in smokers and dependent cocaine users after quitting. Vaccines have a number of potential advantages over existing drug treatments: they sequester drugs in the bloodstream, preventing them from entering the brain; they may have fewer side-effects than drugs that act on the CNS; and they may have better rates of patient compliance than oral drugs.

Other possible uses of vaccines are more controversial. This includes the legal coercion or compulsion of cocaine-dependent people to be vaccinated. The preventive use of vaccines in adolescents also needs to be approached with great caution. We should avoid allowing unrealistic expectations about the preventive role of vaccines in adolescence to undermine their potential value as aids to relapse prevention in adult smokers and cocaine users.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 258).

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