

SYMPOSIUM ON DRUGS

Ethical issues in using a cocaine vaccine to treat and prevent cocaine abuse and dependence

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A “cocaine vaccine” is a promising immunotherapeutic approach to treating cocaine dependence which induces the immune system to form antibodies that prevent cocaine from crossing the blood brain barrier to act on receptor sites in the brain. Studies in rats show that cocaine antibodies block cocaine from reaching the brain and prevent the reinstatement of cocaine self administration. A successful phase 1 trial of a human cocaine vaccine has been reported. The most promising application of a cocaine vaccine is to prevent relapse to dependence in abstinent users who voluntarily enter treatment. Any use of a vaccine to treat cocaine addicts under legal coercion raises major ethical issues. If this is done at all, it should be carefully trialled first, and only after considerable clinical experience has been obtained in using the vaccine to treat voluntary patients. There will need to be an informed community debate about what role, if any, a cocaine vaccine may have as a way of preventing cocaine addiction in children and adolescents.

Cocaine is one of the most widely used illicit drugs in the world, with 13 million people reported to have used it globally in 1997.¹ The highest rates of cocaine use are in the USA where in 2000 11.2% of Americans over the age of 12 reported that they had used cocaine at some time in their lives and 800 000 (0.4%) were weekly users.² Cocaine use has been less common in Europe where the proportion of adults who reported the lifetime cocaine use in the late 1990s varied between 1% and 3.7%.³

Regular cocaine use can adversely affect users in a number of ways. As many as one in six who use cocaine become dependent on it in the sense of finding it hard to cease using or to control the amount they use.⁴ In large doses cocaine can cause fatal cardiac arrests, cerebral vascular accidents, seizures, and hyperthermia in healthy young adults and in cocaine addicts.^{5,6} Regular cocaine users have high rates of anxiety and affective disorders^{6,7} and paranoid psychoses.^{6,8} Cocaine injecting is associated with higher rates of HIV infection via needle sharing, and risky sexual behaviour.⁹

There are no pharmacological treatments for cocaine dependence¹⁰ that are as effective as methadone maintenance treatment is for heroin dependence.¹¹ Psychosocial treatments for cocaine dependence all reduce cocaine use but there is substantial treatment dropout and a high rate of relapse to cocaine use after treatment.^{12,13} More effective drug treatments for cocaine dependence would increase treatment retention and reduce relapse.¹¹

THE FEASIBILITY OF A COCAINE VACCINE

A “cocaine vaccine” induces the immune system to form antibodies that bind to cocaine. Combining a protein molecule with cocaine, it provokes the formation of antibodies that bind with the cocaine molecule to form a

complex molecule that is too large to cross the blood brain barrier.^{14,15} In this way a cocaine vaccine intercepts the cocaine molecule in the bloodstream before it can act on dopamine receptor sites in “reward centres” of the brain.¹⁶

Animal studies have demonstrated the feasibility of using a cocaine vaccine to treat cocaine dependence by showing that antibodies can be induced to the cocaine molecule.^{14,15,17–19} When these antibodies are administered to rats, the amount of cocaine that reaches the brain is greatly reduced.¹⁵ “Active immunisation” against cocaine produces more persistent changes in the animal’s immune system^{19,20} which reduce the locomotor effects of cocaine in rats and markedly attenuate the self administration of cocaine, a model of cocaine addiction in humans.^{21,22} The attenuation of self stimulation is related to the dose of cocaine antibody that is administered.²¹

Human trials of a cocaine vaccine

Kosten and colleagues have completed a phase 1 clinical trial of a cocaine vaccine (TA-CD) in humans.^{23,24} The subjects were 34 abstinent cocaine abusers who were treated in a residential treatment programme. Twenty seven patients received three vaccinations at monthly intervals, 24 were followed for three months, and 15 were followed for 12 months postvaccination. Three increasing doses of the cocaine vaccine were well tolerated, producing only mild, short lived adverse reactions at the site of injection. The vaccine induced antibodies to cocaine after the second vaccination and levels increased after the third. Antibody levels were maintained up to two months after the third vaccination but fell rapidly thereafter and returned to baseline at the end of a year.^{23,24} Clinical trials of the efficacy of a cocaine vaccine are now in progress.

POTENTIAL ADVANTAGES AND DISADVANTAGES OF A COCAINE VACCINE

A cocaine vaccine has two potential advantages over existing drug treatments for cocaine dependence. First, it does not require daily dosing. Cocaine antibodies could be given weekly or a vaccine could be administered on two or three occasions to induce antibodies that blocked cocaine’s effects for several months. This should increase treatment compliance and effectiveness.¹⁴

Second, because the antibodies do not act in the brain they can be used in combination with other medications that do, such as antidepressants or anticraving drugs like disulfiram that reduce craving or depression.²⁴ For the same reason, antibodies are likely to have fewer adverse side effects than drugs that do act in the brain, thereby reducing the high rates of discontinuation often seen in other drug treatments for cocaine.¹¹

A third advantage is that the vaccines under trial do not block the effects of cocaine indefinitely. Their effects are not irreversible but will gradually diminish over time and

eventually disappear, unless the patient chooses to have a further course of vaccinations.

A cocaine vaccine also has some potential disadvantages. First, it will not completely block the effects of cocaine in all circumstances. When cocaine is injected or smoked as crack, there may be too little time for antibodies to bind to all of the cocaine that is ingested before it reaches the brain.²⁵ Similarly patients can also circumvent a cocaine vaccine by substantially increasing their usual cocaine dose.²⁵ None the less, under both circumstances the cocaine antibodies will still attenuate the rewarding effects of the cocaine, thereby markedly reducing the chance that a “slip” will mean a return to heavy cocaine use.²⁴

Second, patients can also evade the effects of a cocaine vaccine by using other stimulant or euphoriant drugs instead of cocaine, such as, methamphetamine. This is a limitation of all drug vaccines which are highly specific to the drug against which they are developed. In principle, this problem could be addressed by developing multidrug vaccines for popular combinations of drugs. There may be increased costs in demonstrating the safety and efficacy of multidrug vaccines.

POTENTIAL USES OF A COCAINE VACCINE

Relapse prevention

A cocaine vaccine or antibodies could be used in cocaine dependent persons to prevent relapse to cocaine use after abstinence has been achieved. It would be effective for as long as a sufficient immune response were present to block or attenuate the effects of cocaine. Passive immunisation using antibodies would attenuate the effects of cocaine for some days to weeks in much the same way as the opioid antagonist naltrexone is used to prevent relapse in abstinent alcohol and opioid dependent individuals. The main difference is that the effects of cocaine antibodies would be longer lasting than an oral dose of naltrexone.

Active immunisation by repeated administrations of a cocaine/protein antigen would produce a longer lasting antibody response to cocaine. Its effects would decline over time so booster injections would be required, perhaps every two to three months.²⁴ A cocaine vaccine (or antibodies) would be given as part of a psychosocial treatment programme which addressed skill and personal deficits and comorbid psychiatric disorders that a cocaine dependent patient had—for example, depression, and psychotic symptoms.

USING A COCAINE VACCINE TO TREAT VOLUNTARY PATIENTS

A number of ethical issues would arise in using a cocaine vaccine to treat cocaine dependent people who voluntarily sought treatment, that is, who freely and willingly decided to enter treatment in the absence of any legal duress.

The first ethical issue would be to ensure that patients freely consented to the vaccine in full knowledge of its effects and any risks that its use entailed. Information about the latter would be obtained from clinical trials of the safety and efficacy of a vaccine.

A second ethical issue may arise because antibodies can be detected in the blood of treated patients, thereby potentially raising ethical concerns about privacy and discrimination.²⁶ Because the community strongly disapproves of cocaine dependence, the concern has been expressed that the loss of privacy by a recovering cocaine addict may lead to social stigmatisation and ostracism by people they know or work with.²⁶ This could adversely affect their employment prospects and recovery. The current use of urine tests for drug metabolites by potential or current employers presents similar concerns.

It is doubtful whether the analytical methods for detecting cocaine antibodies would be commercially available for use in employee drug screens, or whether there would be enough employees receiving cocaine vaccines to make it worthwhile for employers to screen for them. If loss of privacy and discrimination did prove to be a concern any such effects could be minimised by using “passive” rather than “active” immunisation to prevent relapse—for example, by administering antibodies rather than a vaccine. The antibodies would disappear over a period of weeks but at the price of a shorter period of protection that may reduce treatment effectiveness.

A third ethical issue arises if a cocaine vaccine is approved for therapeutic use, namely, who would have access to the vaccine? Access will depend upon how much it costs and who pays for the vaccine—for example, the patient, a third party such as the government or health insurer, or some combination of patient and third party. If a cocaine vaccine proves to be a costly treatment for which patients must pay, then indigent and poor patients would be denied access to its benefits. A public subsidy may be necessary for the vaccine to have a public health impact on cocaine related health problems because many cocaine dependent people may not be able to pay for a vaccine.

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. The treatment is provided under the threat of imprisonment if the person fails to comply.^{27–28} Its main justification is that the offender’s chance of reoffending will be reduced if their drug dependence is treated.^{29–30}

A consensus view of a World Health Organisation panel³¹ was that compulsory treatment was legally and ethically justified if and only if: (1) the rights of the individuals were protected by “due process”, and (2) effective and humane treatment was provided. In the absence of due process, coerced treatment could become de facto imprisonment without judicial oversight. In the absence of humane and effective treatment, coerced drug treatment could become a cost cutting exercise to reduce prison overcrowding.

Offenders should be allowed two “constrained choices”.³² The first choice is whether to participate in drug treatment. If they declined treatment, they would be dealt with by the criminal justice system in the same way as anyone charged with their offence. The second choice for those who agree to drug treatment is a choice of the type of treatment that they receive. There is some empirical support for the view that coerced treatment that requires some “voluntary interest” by the offender is more effective.²⁹

An ethically defensible use of a cocaine vaccine under coercion would use the threat of imprisonment as an incentive for treatment entry, and fear of return to prison as a reason for complying with drug treatment. Offenders would be given a choice of treatment or not, and, a cocaine vaccine would be one of the treatments from which they could choose. If a cocaine vaccine were used in this way, its safety, effectiveness, and cost effectiveness would have to be rigorously evaluated.³⁰ We would also need realistic expectations about its efficacy since a vaccine can be subverted by increasing the cocaine dose or using other stimulant drugs.^{14–24} Any coerced use of a cocaine vaccine should accordingly be implemented cautiously and rigorously evaluated, and only after considerable experience in using should it be used to treat voluntary patients.

PREVENTIVE USE OF A COCAINE VACCINE

In principle, a cocaine vaccine could be used to prevent cocaine dependence if it were administered to persons who had not used cocaine but who were at high risk of doing so, if—for example, they had a family history of cocaine problems and ready access to the drug. If a cocaine vaccine proves safe and effective in treating cocaine dependence, it is likely that some parents will want to use it to prevent their children from becoming cocaine dependent.²⁶

Given that cocaine and other drug use may begin in the early teens, the preventive use of a cocaine vaccine would involve administering the vaccine to minors. This use of a cocaine vaccine would be ethically contentious if children were pressured into immunisation. Some will argue that since parents already make choices on behalf of their children which affect their lives as adults—for example, their diet and education—vaccination against cocaine is another decision that parents could make.^{26–33} The courts seem to agree in the case where a child assents to a parent's wishes for medical treatment and the treatment is safe and effective.

Even if we allow that parents have such rights, there are a number of concerns about such a proposal. First, its attractiveness probably depends upon a mistaken belief about the efficacy of a vaccine. The term “cocaine vaccine” raises the expectation that vaccination will provide a young person with lifelong immunity to the effects of cocaine. It would not: booster injections would probably be required, perhaps as often as once every two or three months throughout adolescence.²⁴ This technical limitation could be overcome, in principle, but at the cost of raising concerns about a vaccine that was potentially irreversible or difficult to reverse.

Second, there are a number of concerns about safety. If those who were vaccinated attempted to circumvent the vaccine by using larger doses of the drug they would increase the risks of its adverse effects. There is also the possibility that vaccination may be counterproductive if adolescents who had been vaccinated were thereby prompted to test the efficacy of the vaccine by using cocaine. If they tested it by using large doses there would be the risk that as the level of antibodies declined over time, using the same high dose that was initially required to overcome the immune blockade could produce a severe adverse effect, such as a stroke or cardiac arrhythmia.^{9–6}

Third, it would be costly to give repeated vaccinations every two or three months throughout adolescence. These costs would probably preclude public funding of universal cocaine vaccination. If, as a consequence, access to cocaine vaccination was on the basis of capacity to pay, the result may be that the children who are most likely to be vaccinated are those at the lowest risk of using cocaine.

For all these reasons, any preventive use of a cocaine vaccine in adolescence should only be implemented, if at all, after careful ethical analysis and community debate. It would be wise to do so in the light of considerable experience of using it to treat consenting adults to see what misadventures may follow any attempts that patients may make to evade the immune blockade.

CONCLUSIONS AND IMPLICATIONS

A cocaine vaccine has the following potential advantages over existing drug treatments for cocaine dependence: it blocks cocaine from entering the brain; it may have fewer side effects than drugs that act on the brain, and it may produce better patient compliance and treatment outcome than existing oral drugs.

If a cocaine vaccine proves effective in human clinical trials, it will be ethically justifiable to use it to treat cocaine dependent patients who have given free and informed

consent to its use. The major ethical issues are ensuring that the treatment is safe and effective and that patients give free and informed consent to treatment. Protection of patient privacy and confidentiality is not likely to be a major concern. The major uncertainties about its safety arise because it will not completely block the effects of smoked or injected cocaine. Patients who attempt to subvert its effects by increasing their cocaine dose or using other stimulant drugs may put themselves at risk of adverse drug effects. The effectiveness of a vaccine may be improved by combining it with pharmacotherapies that reduce craving for cocaine or treat comorbid depression.

The use of a cocaine vaccine to treat legally coerced clients heightens ethical concerns about efficacy and safety. When used to treat legally coerced patients a cocaine vaccine is likely to be of more limited efficacy because these patients are more likely to attempt to evade its effects and in the process expose themselves to any adverse drug effects. It is arguably ethical to use a cocaine vaccine under legal coercion if offenders can choose (a) whether or not to accept treatment and (b) the type of treatment that they accept. Any coerced use of a cocaine vaccine should be done cautiously and only after considerable experience of its use with voluntary patients to assess the risk of misadventure from attempts to overcome the immune blockade.

The preventive use of a cocaine vaccine is also likely to be ethically contentious. Among the ethical issues raised would be whether parents should be able to consent to its use in their children; the possibility of counterproductive adverse effects of its use, and issues of access to what may be an expensive intervention. Any trials of its preventive use should be preceded by public debate and extensive clinical experience in voluntary patients who are cocaine dependent.

Existing drug vaccines have been developed to block the effects of a drug of dependence for a limited time period, typically some months. This is longer than the action of oral medication but similar to that of depot formulations of drugs (those that are implanted under the skin to slowly release an active substance). While this is their duration of action, drug vaccines raise similar ethical issues to those raised by long acting drugs that affect behaviour, such as, depot neuroleptic drugs and antidepressant medication. If longer acting vaccines were developed, particularly vaccines whose effects were either irreversible or lasted a substantial fraction of a normal life span, then such vaccines would raise ethical issues that were more like those raised by neurosurgical interventions to change behaviour.

The ethical issues raised by a cocaine vaccine have broader implications in two respects. First and most directly, the same immunological approach could be used to block the action of any psychoactive drug.³⁴ Indeed, a nicotine vaccine is under development,^{34–35} and animal studies showed the feasibility of a heroin vaccine over thirty years ago.³⁴ The drug vaccines that are under development are primarily intended to treat drug dependence in voluntary patients but they could also be used under legal coercion, and they could also be used for preventive purposes. The potential use under legal coercion is most obvious in the case of heroin, methamphetamine, and phencyclidine (PCP) because the use of these drugs is illegal and a substantial proportion of their users are involved in the criminal justice system in part because of criminal activities to fund their drug use. The use of drug vaccines in these cases would raise the same ethical issues as a cocaine vaccine.

More speculatively, immunotherapies may be developed to modify other socially disapproved forms of behaviour. If the same brain reward systems are involved in binge eating and compulsive gambling—for example, then the rewarding effects of these activities might be attenuated by vaccines

that block precursor chemicals in the bloodstream. We may also need to begin thinking about the ethical issues that may be raised by non-traditional uses of vaccine technology to control behaviour.

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