ETHICAL ISSUES IN TRIALING AND USING A COCAINE VACCINE TO TREAT AND PREVENT COCAINE DEPENDENCE

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Executive Summary

Cocaine dependence is a serious personal and public health issue in some developed countries and is becoming one in some developing countries. It is difficult to treat because of the modest effectiveness of existing psychosocial and pharmacological treatments.

A cocaine vaccine acts on cocaine molecules in the bloodstream to substantially reduce the amount of cocaine that crosses the blood-brain barrier to act on receptors in the brain. It involves administering a complex molecule of cocaine and immunogenic proteins which induces the formation of antibodies that bind to cocaine and its psychoactive metabolites. These molecular complexes are too large to cross the blood-brain barrier and so prevent cocaine from reaching the brain.

They are two other types of Peripheral Cocaine Blocking Agent (PCBA) that act in similar ways to a cocaine vaccine. A second type of PCBA increases the amount or the level of activity of naturally occurring enzymes that metabolise cocaine in the blood and liver. Any cocaine that is administered while these enzymes are present in the blood is metabolised before it reaches the brain. The third type of PCBA involves using a cocaine-protein complex to induce an antibody to cocaine that accelerates the metabolism of cocaine in plasma, thereby reducing the amount of cocaine that crosses the blood-brain barrier.

A cocaine vaccine and the other PCBAs have a number of potential advantages over existing drug treatments, namely, they block cocaine from entering the brain, they may have fewer side effects, and they are likely to have better rates of patient compliance because they are administered less often than oral drugs.

The evidence of their effectiveness is confined to studies using animal models of cocaine dependence. These results, and the results of one phase 1 clinical trial, are sufficiently promising to warrant human trials of efficacy. Human clinical trials of the efficacy and safety of a cocaine vaccine will need to address the standard ethical issues of informed consent and rigorous trial design.

If a cocaine vaccine proves effective in human clinical trials, the least ethically problematic use will be using cocaine antibodies or cocaine-metabolising enzymes to manage cocaine toxicity and overdose.

A cocaine vaccine will not be a stand alone treatment for cocaine dependence. When used in the context of good psychosocial care it may improve abstinence rates but it is unlikely to completely block the effects of smoked or injected cocaine. Patients will be able to over-ride its effects by increasing their dose of cocaine or by using other stimulant drugs. The effectiveness of a vaccine may be improved by using it in combination with other PCBAs and with other pharmacotherapies for cocaine dependence.

The use of a cocaine vaccine to treat cocaine dependent persons will be ethically acceptable when used in voluntary patients who have given free and informed consent to their use. In this setting, an abstinent cocaine dependent patient may either be "passive immunised" with cocaine antibodies or actively immunised against cocaine

in order to reduce their risk of relapsing to cocaine use. The major ethical issues with this use of a vaccine or antibodies is in ensuring that patients give free and informed consent to treatment.

One possible ethical issue with a cocaine vaccine will be in protecting patient privacy and preventing discrimination against recovering addicts on the basis of cocaine antibody in their blood. This problem is not wholly new: similar issues have been addressed in methadone maintenance treatment for heroin dependence and with HIV seropositivity in injecting drug users. Similar legislative and public education approaches may minimise these problems with a vaccine. The severity of the problem may also be reduced by using "passive" immunisation with monoclonal cocaine antibodies that disappear from the body after some weeks.

The use of a cocaine vaccine to treat legally coerced clients poses more ethical problems. It is arguably ethical to use it in this way if and only if offenders are offered constrained choices of (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 clinical experience with its use with voluntary patients. Any use in patients under legal coercion should be on a trial basis with rigorous evaluation of its safety, effectiveness and cost-effectiveness. The evaluation would also need to examine any adverse health, social or ethical consequences that it may have before it was more widely implemented.

The preventive use of a cocaine vaccine is even more ethically contentious. Any trials of its preventive use should be preceded by extensive clinical experience with a cocaine vaccine in voluntary patients who are cocaine dependent. A higher standard of safety will also need to be met if a vaccine is to be used preventively. Important ethical issues are also raised by such a use, namely, the capacity of minors to consent to its use, the rights of parents to make decisions about vaccination on behalf or their children, the protection of privacy, and the prevention of discrimination against children who have been vaccinated.

1. Introduction

In this paper we discuss the ethical implications of using a cocaine vaccine and other peripheral cocaine-blocking agents (PCBAs) to treat and prevent cocaine dependence. We begin by outlining the reasons for this approach to treatment. We then consider the ethical issues raised by trialing PCBAs to treat persons who are cocaine dependent. We then discuss the ethical issues that are likely to arise in using them to treat cocaine dependence if a cocaine vaccine and other PCBAs prove to be safe and effective in clinical trials. We consider the ethical issues raised by using PCBAs to treat legally coerced patients and the ethical and policy issues raised by the potential use of these agents to prevent cocaine dependence in children and adolescents.

2. **Why Develop Pharmacological Treatments for Cocaine Dependence?**

2.1 Prevalence of use

After cannabis, **c**ocaine is one of the most widely used illicit drugs in developed and developing societies, with 13 million people estimated to have used cocaine globally in 1997 (UNDCP, 1997). The highest rates of reported cocaine use, and the best data on trends in cocaine use, come from the USA. Over the past two decades rates of cocaine use in the USA increased from the mid 1970s until 1985 when 5.7 million Americans aged 12 years and older reported using cocaine in the past month. Rates of cocaine use in the past month have declined steadily since 1985. In 2000, 11..2% of Americans over the age of 12 reported that they had used cocaine at some time in their lives and 0.4% (800,000 people) reported weekly cocaine use (SAMHSA, 2001).

The reported prevalence of cocaine use in other developed societies is much lower than that in the USA. In Europe, for example, rates of lifetime cocaine use in the late 1990s varied between 3.7% of adults in Spain and less than 1% in Belgium, Finland and Sweden (EMCDDA, 1999) compared to 11.2% among American adults in 2000 (SASMSHA, 2001). Rates of cocaine use in Australia resemble those in Europe, with 4.3% of adults reporting lifetime use (Darke et al, 2000).

The use of cocaine is likely to be lower in developing societies but the poor quality of the available data makes it difficult to be sure (UNDCP, 1997). There probably has been an increase in cocaine use in some developing countries in recent years but it is difficult to estimate the size of the increase (United Nations Commission on Narcotic Drugs, 2000). The region with highest rates of cocaine use among developing societies is likely to be Central and South America because of their proximity to source countries for cocaine.

2.2 The Harms Caused by Cocaine Use

Most cocaine use is infrequent but regular cocaine use (monthly or more frequently) can be a major public health problem. Regular cocaine users who inject cocaine or smoke crack cocaine are especially likely to develop dependence and to experience problems related to their cocaine use (Platt, 1997). In the USA it has been estimated that one in a six of those who ever use cocaine become dependent on the drug (Anthony et al, 1994). High rates of cocaine dependence are found among persons

treated for alcohol and drug problems and among arrestees in the USA (Anglin and Perrochet, 1998).

In large doses cocaine is cardiotoxic in both cocaine naïve and tolerant individuals (Platt, 1997; Vasica and Tennant, 2002). The vasoconstrictor effects of cocaine in large doses places great strains on the cardiovascular system that can cause fatal cardiac arrests, cerebral vascular accidents, seizures and hyperthermia in healthy young adults (Majewska, 1996; Platt, 1997; Vasica and Tennant, 2002). There is no antidote to cocaine overdose as there is for an overdose of heroin (Platt, 1997).

Regular cocaine users experience high rates of psychiatric disorder. In the United States, regular cocaine users report high rates of anxiety and affective disorders (Gawan and Ellinwood, 1988; Platt, 1997). The repeated use of large doses of cocaine can also produce a paranoid psychosis (Majewska, 1996; Manschreck *et al*, 1988; Platt, 1997; Satel & Edell 1991). Persons who are acutely intoxicated by cocaine can become violent, especially those who develop a paranoid psychosis (Platt, 1997). Animal studies suggest that cocaine use may be neurotoxic in large doses, that is, it can produce permanent changes in the brain and neurotransmitter systems (Majewska, 1996; Platt, 1997). It is unclear whether it is also neurotoxic in humans.

Cocaine injecting, either on its own or in combination with heroin (`speedballs'), is associated with more frequent injection, needle sharing, increased sexual risk-taking, and HIV infection (Chaisson *et al*, 1989; Schoembaum *et al*, 1989). An association between cocaine use and HIV risk-taking has been reported in Europe (Torrens *et al*, 1991), Australia (Darke *et al*, 1992), and the USA (Chaisson *et al*, 1989).

The link between cocaine use and HIV risk is not restricted to those who inject cocaine. Crack smoking has been linked to higher levels of needle risk, sexual risk-taking and HIV infection (Grella *et al*, 1995, Chiasson *et al*, 1991; Chirgwin *et al*, 1991; DesJarlais *et al*, 1992). Two mechanisms probably underlie the relationship between cocaine use and HIV infection. First, the short half-life of cocaine promotes a much higher frequency of injecting than that seen in heroin injectors. Second, cocaine itself, disinhibits and stimulates users, encouraging them to take greater risks with sexual activity and needle use (Darke *et al*, 2000).

2.3 The Treatment of Cocaine Dependence

Psychosocial treatments for cocaine dependence are of limited effectiveness. Treatments such as therapeutic communities, cognitive behavioural treatments, contingency management and 12-step based self help approaches, benefit cocaine dependent persons in reducing rates of cocaine use and improving their health and well being but around a third drop our of treatment (Simpson, Joe and Broome, 2002) and 21-25% continue to use cocaine weekly one to five years after treatment (Simpson et al, 1999; Simpson, Joe and Broome, 2002)). It would be desirable to have a pharmacological treatment to add to existing psychosocial treatments to reduce treatment drop out and relapse to cocaine use.

2.4 Summary

The reasons for seeking a pharmacological treatment of cocaine dependence can be briefly summarised as follows. First, cocaine is one of the most widely used illicit drugs after cannabis in many developed countries and its use appears to be rising in some developed and developing societies. The USA has had the highest rates of cocaine use over the past several decades although rates of use have been declining for the past decade. Second, regular cocaine users experience a range of serious adverse health effects, including dependence, fatal overdose, depression, psychosis, violence, and HIV infection. Third, the effectiveness of psychosocial treatments would be enhanced by the addition or a pharmacological treatment that would reduce treatment drop out and relapse to cocaine use. Improved treatment would enable the health care system to respond more effectively to requests for help from cocaine dependent persons.

3. **Why Develop A Cocaine Vaccine?**

A major reason for developing a cocaine vaccine has been the failure to develop effective pharmacological treatments for cocaine dependence. Several decades of research have failed to produce pharmacological treatments for cocaine dependence that are as effective as methadone maintenance treatment is for heroin dependence (Kreek, 1997; McCance, 1997; Nunes, 1997).

One approach to developing pharmacotherapies for cocaine dependence has been to develop longer-acting agonist drugs that act on the same molecular targets as cocaine without producing its euphoric effects (e.g. methylphenidate) (Kreek, 1997). This approach was inspired by the use of methadone in heroin dependence. A second approach has been to search for drugs that bind to the same receptor sites as cocaine while blocking its rewarding and euphoric effects (McCance, 1997). This approach was inspired by the use of opioid antagonists, such as naltrexone, to treat heroin dependence (McCance, 1997). A third approach has been to search for drugs that indirectly change the effects that cocaine has on the brain by acting on other neurotransmitter systems, such as the serotonergic system (e.g. fluoxetine) (McCance, 1997)

None of these approaches has produced an effective pharmacotherapy for cocaine dependence (de Lima *et al*, 2001; 2002; Platt, 1997; Soares *et al*, 2001a,b). This probably reflects a number of factors. One is that cocaine affects multiple neurotransmitter systems, rather than primarily acting on one receptor system, as seems to be the case with the opioids (Platt, 1997). This has made it difficult to develop non-euphoric agonists or antagonists that block the effects of cocaine (De Prada, Winger and Landry, 2000). A second possibility is that the available agents may not be blocking the right cocaine receptor sites or they may not be very effective blockers of cocaine's effects (McCance, 1997).

The lack of success with these approaches has prompted a search for a very different pharmacological approach to the treatment of cocaine dependence. This approach has been described as "pharmacokinetic" (Gorelick, 1997) because it aims to reduce the amount of cocaine that reaches the brain by intercepting the cocaine molecule in the

bloodstream. This approach which includes a cocaine vaccine has been described as the class of "peripheral cocaine-blocking agents" (Sparenborg *et al*, 1997).

The same immunological approach can be potentially applied to the treatment of dependence on a range of psychoactive drugs. The feasibility of using drug vaccines to block drug effects was originally demonstrated in the early 1970s in rhesus monkeys that had been trained to self-administer heroin (Bonese, Wainer, Fitch et al, 1974). The potential to use a nicotine vaccine to treat nicotine dependence is also currently being actively explored in animal studies (Hall, 2002; Vocci and Chiang, 2001). Many of the same issues raised by a cocaine vaccine will apply to the therapeutic use of other drug vaccines, such as nicotine (Hall, 2002). One exception will be the possible use of vaccines under legal coercion, an issue which arises for those who are dependent on illegal drugs who engage in criminal activities to finance their drug use.

4. What are Peripheral Cocaine Blocking Agents?

A cocaine vaccine shares a similar rationale to two other types of "peripheral cocaine blocking agents" (PCBAs) (Sparenborg *et al*, 1997). All three approaches obviate the need to block multiple receptor sites for cocaine in the brain by acting on cocaine molecules in the bloodstream. They all aim to substantially reduce the amount of cocaine that crosses the blood-brain barrier to act on receptor sites in the brain (Sparenborg *et al*, 1997).

A cocaine vaccine is the first type of PCBA. It involves administering a complex molecule of cocaine and proteins which induces the formation of antibodies that bind to cocaine and its psychoactive metabolites. These molecular complexes are too large to cross the blood-brain barrier and so prevent cocaine from reaching the brain (Fox, 1997; Fox *et al*, 1996).

A second type of PCBA increases either the amount or the level of activity of naturally occurring enzymes that metabolise cocaine in the blood and liver. This is achieved by administering large doses of naturally occurring enzymes (e.g. butyryl-cholinesterase BchE), or analogues which metabolise cocaine (Gorelick, 1997). Any cocaine that is administered while these enzymes are present in the blood is metabolised before it reaches the brain.

A third type of PCBA combines elements of the first two. It involves using a cocaine protein complex to induce an antibody to cocaine that catalyses or accelerates the metabolism of cocaine in plasma, thereby reducing the amount of cocaine that crosses the blood-brain barrier (Landry, 1997; Mets *et al*, 1998).

There is a possible variant of both the first and third approaches that does not involve administering a vaccine to a person with cocaine dependence. This variant would administer antibodies to cocaine ("monoclonal antibodies") that blocked cocaine from reaching the brain while they remained in circulation. Unlike active vaccination, the person's immune system would not be altered and the antibodies would disappear over a period of weeks.

4.1 A Question of Terminology

The phrase "peripheral cocaine-blocking agents" is the most accurate generic description of these approaches to treating cocaine dependence. It does, however, have the disadvantage that it is a four word phrase with a not very felicitous, mnemonic or memorable acronym. The term "cocaine vaccine", by contrast, is simpler and for that reason more likely to become the term that is popularly used to describe the PCBA approach to treating cocaine (and other forms of drug) dependence (Kaebnick, 2000).

Some would argue that the phrase a "cocaine vaccine" extends the conventional meaning of a "vaccine" in unhelpful ways because a cocaine vaccine does not prevent an infectious disease by inducing immunity to its causative microorganism (Nossal, 1999). There are a number of precedents for broadening the use of the term "vaccine" in this way. First, the use of "vaccination" as a synonym for all types of immunisation is already an extension of the original usage which described Jenner's use of cowpox (vaccinia) to prevent smallpox in humans (Nossal, 1999). Second, the term "vaccine" has been more recently extended to immunotherapies for non-infectious diseases. There are, for example, vaccines under development "against": cancer, the rejection of organ transplants, allergies, heart disease, and pregnancy (Nossal, 1999). Using "vaccine" to describe an immunological treatment of a behavioural disorder stretches conventional usage further still but this extension is arguably defensible because the immune system is being used therapeutically to block the effects of cocaine.

There is nonetheless a major drawback with using the term vaccine for treatments of cocaine (or other forms of drug dependence), namely, that it raises the unrealistic expectation that individuals can be vaccinated for life against the effects of cocaine (or other drugs). The phrase "immunotherapy" would provide a better description of the approach but we seem to be stuck, for better or worse, with the term "vaccine". In the rest of the paper we accordingly use the phrase "cocaine vaccine" to describe all PCBAs. When necessary, we will use the terms "active" and "passive" vaccination to distinguish between uses of this approach that do and do not produce enduring changes in the immune system of the person.

5. The Feasibility of a Cocaine Vaccine

Evidence for the feasibility of using these three approaches to treating cocaine dependence has so far come from animal studies. These studies provide a "proof of the concept" for the therapeutic use of a cocaine vaccine in humans in the following ways.

First, animal studies have shown that it is possible to induce antibodies to the cocaine molecule by attaching it to protein to form antigen complexes (e.g. Carrera *et al*, 2000, 2001; Fox *et al*, 1996, Fox, 1997; Johnson and Ettinger, 2000).

Second, animals studies shown that when these antibodies combine with cocaine and its psychoactive metabolites, the resulting complex molecule is too large to cross the blood-brain barrier, preventing it from exerting its effects on receptors in the brain (Fox *et al*, 1996). When cocaine antibodies are administered to rats, there is a substantial increase in the amount of cocaine that is retained in body plasma and

therefore a marked reduction in the amount of cocaine that reaches the brain (Fox *et al*, 1996). This is called "passive immunisation" because the immune systems of these animals have not been induced to manufacture antibodies. Its effects disappear as the antibodies are broken down.

Third, active immunisation of animals against cocaine involves producing more persistent changes in their immune systems by inducing the production of antibodies to the cocaine-protein complex. Studies have shown that active immunisation (Carrera *et al*, 1995; Johnson and Etttinger, 2000) also reduce the locomotor effects of cocaine in rats and markedly attenuates the self-administration of cocaine by rats, an animal model of cocaine addiction in humans.

Fifth, a number of recent animal studies have also provided proof of concept for catalytic antibodies and enzymes that metabolise cocaine. These studies have been shown that both approaches reduce cocaine overdose and the reinforcing effects of cocaine in rats (Baird *et al*, 2000; Mets *et al*, 1998).

The animal studies show, in summary, that cocaine antibodies can be induced that reduce the amount of cocaine that reaches animals' brains, reduce the locomotor stimulating effects of cocaine, and reduce the amount of cocaine that is used by animals in self-administration models of cocaine dependence

6. Potential Human Uses of a Cocaine Vaccine

There is very limited human experience with a cocaine vaccine. There is one phase 1 clinical trial of a cocaine vaccine (TA-CD) in humans (Kosten et al, 2000; 2002). The subjects were 34 abstinent cocaine abusers who were being treated in a residential treatment program. 27 patients completed a course of three vaccinations given at monthly intervals, 24 were followed for 3 months, and 15 were followed for 12 months post-vaccination.

This study demonstrated that three increasing doses of the cocaine vaccine were well tolerated, with only mild and short lived adverse reactions at the site of injection. The vaccine induced antibodies to cocaine after the second vaccination and their levels increased after the third. Antibody levels were maintained up to two months after the last vaccination but fell rapidly thereafter and had returned to baseline by the end of a year (Kosten *et al*, 2000; 2002). Clinical trials of the efficacy of a cocaine vaccine are in progress but it will be some time before their results are available. In the absence of human research, our analysis of ethical issues raised by the human use of a cocaine vaccine must be based upon projections from the results of animal studies.

6.1 Reversal of Cocaine Overdose

Acute cocaine toxicity could be treated using either cocaine antibodies or administering large doses of cocaine-metabolising enzymes. The antibodies or enzymes would bind to cocaine circulating in plasma and prevent it from acting on brain receptors. This use raises the fewest ethical and policy issues because it would be lifesaving and its effects would be short-term. The major ethical issues would be in ensuring that it is a safe and effective way of using antibodies or other PCBAs. Because individuals may be unconscious or confused, and so unable to consent to

their use, clinical trials would need to ensure that specified criteria and proxy consent was used to protect patients. But this is not an insuperable problem given the seriousness of cocaine toxicity, and the lack of alternative treatments for these serious acute complications of cocaine use.

6.2 Relapse Prevention

A cocaine vaccine could be used in cocaine dependent persons to prevent relapse to cocaine use after abstinence has been achieved. Prevention of relapse to cocaine use could be accomplished by either "passive" or "active" immunisation.

In passive immunisation antibodies would be given to a patient so that the effects of any cocaine that they used would be attenuated. This protection might last for some weeks. Cocaine-metabolising enzymes would be used much like passive immunization: their effects would only last while the enzymes were present. This period could possibly be extended by using slow-release forms (e.g. skin patches or implants) that could block the effects of cocaine for weeks and possibly months.

In active immunisation the person could be immunised against cocaine by repeated administrations of a cocaine-protein antigen that would produce a longer-lasting antibody response to cocaine. The effects of active immunisation could, in principle, be permanent, although in practice cocaine antibody levels would probably decline over time and may eventually not protect against cocaine use without booster injections.

Any of the three types of PCBAs could be used in the longer term to reduce relapse to cocaine use in persons who had achieved abstinence and who, on the basis of previous experience, felt vulnerable to relapse in the face of temptation. This use would have parallels to the use of naltrexone to prevent relapse in abstinent opioid dependent individuals.

In all of these uses, a cocaine vaccine would be provided in the context of psychosocial treatment to address skill and personal deficits and comorbid psychiatric problems that the patient may have. A cocaine vaccine would therefore *not* be a stand-alone treatment for cocaine dependence. It would probably also be used in combination with other pharmacological treatments e.g. to reduce craving for cocaine or to treat comorbid depression or alcohol dependence.

6.3 Prevention of Cocaine Dependence

A more speculative use for a cocaine vaccine would be to prevent cocaine abuse and dependence. This could involve administering a cocaine vaccine to persons who had not used cocaine but who were adjudged to be at high risk of doing so, e.g. because of a family history of cocaine problems or ready access to the drug. Given that cocaine and other drug use may begin in the early teens, this would involve administering the vaccine to minors. The ethical issues raised by this use are discussed below.

7. Potential Advantages of a Cocaine Vaccine

A cocaine vaccine has a number of potential advantages over existing pharmacotherapies for cocaine dependence.

First, a cocaine vaccine would need to be given much less often than the daily dosing that is required with oral medications. Cocaine antibodies or metabolising enzymes could be given weekly or less often while a vaccine could be administered on two or three occasions with effects that lasted for some months. The less frequent dosing would reduce the problem of poor compliance with conventional oral cocaine pharmacotherapies where there is often a high drop out early in treatment.

Second, because the three different types of PCBA act by different mechanisms they could in principle be used in combination with each other. This would allow their therapeutic effects to add to or amplify each other.

Third, PCBAs do not cross the blood brain barrier and so do not act in the brain. This means that they can also be used in combination with other medications that do act in the brain, such as antidepressants. It also means that they should have fewer adverse side effects than drugs that do act in the brain. This should also reduce the high rates of discontinuation of treatment that often occur when dopamine agonist and antagonists are used to treat cocaine dependence (McCance, 1997).

8. Potential Disadvantages of a Cocaine Vaccine

A cocaine vaccine has the following potential disadvantages. First, it is unlikely to be completely effective in blocking the effects of cocaine. This is especially likely when cocaine is injected or smoked as crack because there is too little time between use by these routes and cocaine entering the brain for antibodies to bind to, metabolise or catalyse all of the cocaine (Wise and Ranaldi, 1996). However, a cocaine vaccine may not need to be perfect to be clinically useful: attenuation of the rewarding effects of cocaine may be enough to substantially reduce rates of relapse. For example, clinical experience with the opioid antagonist naltrexone in the treatment of alcohol dependence has shown that incomplete attenuation of the euphoric effects of alcohol still reduces relapse to dependent drinking (Streeton and Whelan, 2001; Volpicelli, 2001).

A second potential difficulty is that a cocaine vaccine can be circumvented if patients increase their cocaine dose to overcome the peripheral blockade (Wise and Ranaldi, 1996). The increases in dose required may be substantial, making cocaine much more expensive to use and increasing the adverse effects of cocaine. The blockade may also be evaded by using other stimulant or euphoriant drugs instead of cocaine. The impact of this behaviour can be reduced by appropriate patient selection, using behavioural methods to motivate patients and maximise patient compliance. Compliance could also be increased by greater patient supervision, and possibly by legal coercion. The latter possibility raises important ethical and policy issues that are discussed below.

A third potential difficulty with a cocaine vaccine is that the antibodies to cocaine (or cocaine metabolising enzymes) can be detected by blood testing (Cohen, 1997). Their presence would indicate that the person was being treated, or had been treated for

cocaine dependence (Cohen, 1997). This raises concerns about patient privacy and discrimination, both of which are discussed below. This would be less of a problem with "passive immunisation" because monoclonal antibodies would disappear from the body, as would enzymes that metabolise cocaine.

ETHICAL ISSUES

9. Trialing a Cocaine Vaccine to Establish its Safety and Efficacy

Since the Nuremberg trials it has been generally accepted that people should only participate in clinical trials when the study addresses important questions, its benefits to participants outweigh its risks, any risks are justifiable, and the individual gives free and informed consent to participate in the trial (Beauchamp and Childress, 2001; Jonsen, 1998; National Bioethics Advisory Commission, 2001). We have outlined above why it is worth using a vaccine to improve the treatment of cocaine dependence; the remainder of the discussion deals with the other ethical requirements.

In most developed countries, national ethical codes set out ethical obligations for investigators and these guidelines must be followed for a clinical trial to be ethically and scientifically legitimate. Although conditions for ethical approval may differ in detail from country to country, a basic set of ethical principles is found in most national guidelines (Brody, 1998). These include, for example, independent ethical review of research proposals, respect for patient privacy, informed consent to participate and special protection for vulnerable participants (e.g. physically or cognitively impaired patients, the terminally ill, children, ethnic minorities, prisoners etc.) (Brody, 1998).

9.1 Independent Ethical Review of Risks and Benefits

In order for any clinical trial to proceed, investigators must obtain approval from an independent ethical review committee, usually an institutional review (IRB) committee. An independent review of a study protocol provides a disinterested, independent assessment of whether the benefits of the proposed trial outweigh any risks it poses to participants. The likely benefits of an effective human cocaine vaccine to persons with cocaine dependence have been outlined above. The acute risks of a cocaine vaccine in humans who are cocaine dependent are unknown but any human use will be preceded by animal studies and phase 1 trials of safety. In these circumstances, it is arguably the case that the likely benefits of a cocaine vaccine probably outweigh its risks. Nonetheless, uncertainty about longer-term risks would need to be communicated to the participants in the study. There would also need to be close monitoring of adverse events and medical care promptly given to treat any adverse outcomes.

9.2 Informed Consent

Informed consent to participate in a clinical trial is mandatory under the Nuremberg Code. It involves asking the research subject to give consent to participate after they have been given a detailed discussion of the study protocol and the events that will occur during the trial (e.g. assessment, randomisation, treatment, follow up). They

also need to be told about any adverse events that may occur. The participation of persons under the age of eighteen would require the consent of a parent or guardian.

The inclusion of cognitively impaired persons in a trial may require special consideration. Consent may need to be obtained from a surrogate who makes a decision on behalf of the impaired research subject. Care would need to be taken to ensure that subjects were not at the time of giving consent under the influence of cocaine or other drugs that may hinder rational decision-making. These considerations are accepted by researchers in the conduct of their work and are required by national ethical guidelines for research involving human beings in most developed countries.

All forms of consent must be given after the participants are informed of what their involvement in the research will require of them. Research participants should have time to reflect on and consider their obligations *before* providing written consent. A trial must allow participants to withdraw at any time and this option must be given to participants at all stages of the research. A subject's decision to withdraw must be respected and subjects must not suffer any consequences for withdrawing, such as, refusal of routine counselling or medical care. The data collected from a participant must be omitted from the final trial if they withdraw from the study.

9.3 Subject Recruitment

An important component of any clinical trial involving human beings is the ethical recruitment, selection and involvement of research subjects in that trial. In recent years, it has become more common to reimburse participants for their involvement in phase 1 clinical trials from which they are unlikely to derive benefit. These reimbursements are usually in the form of movie and/or food vouchers or small amounts of money. The most common justification is that reimbursements maximise initial recruitment and retention of participants in a phase 1 clinical trial. A less common justification is that they may benefit participants. Thus, a meal voucher or a movie ticket offers the participant, in this case a person with cocaine dependence, a chance to eat a good meal or see a movie.

Small reimbursements are offered to compensate participants for the time spent participating in a trial or for their travel expenses. Often, however, reimbursements are interpreted by potential recruits as rewards for participation and by researchers as a way of increasing the number of trial participants. Under these circumstances, vouchers and money serve as inducements for participation rather than a reimbursement for time and travel costs. Ashcroft (2001) argues that inducements are ethically acceptable if the inducement recompenses a participant for the inconvenience of participation and it is *not* seen as a payment for any harm caused (Ashcroft, 2001:265). Because persons who are cocaine dependent are arguably a vulnerable social group it would not be ethical to offer large financial or other in kind inducement to participate in a cocaine vaccine trial. The use of smaller reimbursements to attend for follow up interviews may be more defensible.

9.4 Privacy and Confidentiality

The privacy of trial participants is an ethical obligation that needs to be ensured in a cocaine vaccine trial. With the consent of the individual, the participant's medical history will be required before treatment can proceed. This is usually one of the first stages of recruitment. In many developed countries, it is an ethical requirement to seek permission from relevant institutional gatekeepers to access a participant's medical history. The participant's personal information must not be divulged to any individual or group of individuals without the participant's direct consent and participants' identities should not be identifiable from the published results of the study. These rules are accepted as necessary components of ethical clinical trials by experienced investigators but violations may still occur and so must be guarded against, especially in studying such a stigmatised disorder as cocaine dependence.

9.5 Trial Design

A randomised controlled trial (RCT) is widely accepted as the "gold standard" for treatment evaluation in medicine because it minimises bias in determining which patients receive which treatments (Cochrane, 1972). Evidence from RCTs would also be required for registration of a cocaine vaccine by regulatory authorities in many developed countries, such as the Food and Drug Administration in the USA. Random assignment to treatment is ethically acceptable if trial participants are aware of this fact. They should, in giving informed consent to participate in the trial, also be informed about the characteristics (e.g. active or placebo) and risks of the treatments to which they will be randomly assigned.

The choice of a comparison condition for a cocaine vaccine raises an ethical issue: is it ethically acceptable to compare a cocaine vaccine with a placebo vaccine? It would be arguably *unethical* if a placebo vaccine was the only treatment provided because cocaine dependence is a potentially life-threatening condition in which outcome is poor in the absence of treatment. It would be ethically acceptable, however, to use a placebo vaccine comparison *if and only if* both treatment groups received the best available psychosocial treatment for cocaine dependence. In this design, the study would answer the research question: does adding a cocaine vaccine to standard psychosocial care improve outcome? This is also the most clinically relevant question because a cocaine vaccine would ultimately be used in combination with good quality psychosocial treatment (Fox, 1997).

10. Using a Cocaine Vaccine to Treat Cocaine Dependence in Voluntary Patients

If a controlled clinical trial demonstrates that a cocaine vaccine is safe and effective in the treatment of cocaine dependence, then the voluntary treatment of cocaine dependence using a cocaine vaccine would raise a number of ethical issues.

The first ethical issue would be ensuring that patients freely consented to receive a cocaine vaccine with full knowledge of any risks that its use entailed. Free and informed consent requires that patients are informed about the benefits and potential risks of the treatment and that they are not coerced into or induced to participate in treatment. The question of whether coercion is permissible and if so, under what conditions, is taken up below. These requirements apply to existing pharmacological

treatments for opioid dependence; they would not present any unique problems for the use of passive immunisation against cocaine.

A potentially unique feature of active cocaine vaccination is that it may, in principle, have irreversible consequences, namely, creating antibodies that can be detected in the blood of treated patients for the remainder of their lives. These antibody levels may not be sufficiently high to be therapeutic but the fact that they could be detected raises the ethical issues of privacy and discrimination.

Of special concern is the possible loss of privacy by recovering addicts if employers and insurance companies had access to this information. Employers and insurance companies often obtain detailed personal medical information and, on occasion, blood samples from potential employees or clients. Because the community strongly disapproves of cocaine dependence (Davey, 1994), the loss of privacy by a recovering cocaine addict may lead to embarrassment, at best, and to social stigmatization and ostracism by people in their immediate social environment and the wider community. As a result former cocaine users could be discriminated against in the workplace or community (Cohen, 1997).

Discrimination may arise if workplace based drug testing were to screen for cocaine antibodies before and during employment. A recovering cocaine dependent person would be at risk of losing an employment opportunity if cocaine antibodies are detected in a blood sample. If this information were more widely disseminated to other workers this could have devastating effect on the employment prospects and recovery of the addict. It is uncertain, however, how many employers would go to the considerable expense of testing for cocaine antibodies when many do not routinely screen for drug metabolites.

The risk of loss of privacy could be avoided by accepting Cohen's (1997) proposal that we “institute legal and behavioural changes that preserve privacy and confidentiality" (Cohen, 1997, p 169). This requires a culture that encourages and supports the recovery of persons with drug dependence. Legislation that punishes discriminatory behaviour towards recovering persons with dependence, has been adopted in the case of HIV infected persons; the adoption of a similar approach to persons who have been treated for cocaine dependence would reduce discrimination and protect privacy.

Risks of loss of privacy and discrimination could also be minimised by using “passive” rather than “active’ immunisation to prevent relapse (e.g. by administering antibodies to cocaine rather than a vaccine). This approach would not produce an enduring change in the person’s immune system and the antibodies would disappear over a period of weeks. These advantages would be purchased at the price of a shorter period of protection (without a booster injection) that may reduce treatment effectiveness. This may be a trade off that a patient concerned about privacy was prepared to make; it is a choice that should be offered to patients.

11. The Use of a Cocaine Vaccine in Legally Coerced Patients

The use of a cocaine vaccine under legal coercion needs to be considered (Cohen, 1997) because community concern about this potential use may adversely affect attitudes towards *any* therapeutic use of a cocaine vaccine. The issue accordingly needs to be discussed, even if a cocaine vaccine is a long way from being used in this way. We believe that there are good reasons for caution about the coerced use of a cocaine vaccine. The community does not have much sympathy for offenders who are drug dependent who engage in property and other crimes so we may need to be more conscientious than usual in protecting their legal and moral rights.

11.1 The Rationale for Treatment under Legal Coercion

Legally coerced drug treatment is treatment entered into by persons charged with or convicted of an offence to which their drug dependence has contributed. It is most often provided as an alternative to imprisonment, and treatment usually proceeds under the threat of imprisonment if the person fails to comply (Hall, 1997; Spooner, 2001).

One of the major justifications for treatment under coercion is that it is an effective way of treating offenders' drug dependence that will reduce the likelihood of their re-offending (Gerstein and Harwood, 1990; Inciardi and McBride, 1991). This approach has historically been most often used in the treatment of offenders who are heroin dependent (Leukefeld and Timms, 1988). It has been recently used with cocaine-dependent offenders in US Drug Courts (National Research Council, 2001).

The advent of HIV/AIDS has provided an additional argument for treating rather than imprisoning offenders who are drug dependent. Prisoners who inject drugs are at higher risk of having contracted HIV and hepatitis by needle-sharing prior to imprisonment (Dolan et al, 1996). They are at risk of transmitting these infectious diseases to other inmates by needle sharing and penetrative sexual acts while they in prison (Vlahov and Polk, 1988) and to their sexual partners after their release from prison. Providing drug treatment under coercion in the community is one way of reducing HIV transmission. The correctional and public health arguments for drug treatment under coercion are reinforced by the economic argument that it is less costly to treat offenders who are drug dependent in the community than it is to imprison them (Gerstein and Harwood, 1990).

11.2 Forms of Legal Coercion

Offenders may be coerced into drug treatment in a variety of ways (Gostin, 1991; Spooner et al, 2001). After an offence has been detected the police may decide not to charge the offender if he or she agrees to enter drug treatment. This form of coercion is not generally favoured because it is not under judicial oversight and so it is open to abuse. Coercion into treatment may also occur after an offender has been charged and before a court appearance. A court, for example, may postpone adjudication until treatment has been completed, as happens in some US "drug courts" (General Accounting Office, 1995).

An offender may be coerced into treatment after conviction. If this is done before sentencing, the Court may make completion of treatment a condition of a suspended sentence. Alternatively, an offender may be encouraged to enter drug treatment to help them remain abstinent from illicit drugs while a sentence is suspended. In this case, remaining drug free would be a condition of receiving a noncustodial sentence rather than enrolment in treatment per se. Drug treatment may also be required after part of a sentence has been served: enrolment in drug treatment may be made a condition of release on parole. Alternatively, enrolment in drug treatment may be encouraged as a way of remaining free of illicit drugs while on parole.

The most coercive form of treatment for drug dependence is the "civil commitment" of addicts which has been used in a number of US states over the past 60 years (e.g. the California Civil Addict Program). In civil commitment, an offender was sentenced to enforced treatment for drug dependence in a secure "hospital", often for an extended period. Compulsory hospital treatment was often followed by community based drug treatment under supervision. Failure to comply with treatment or supervision could result in return to a secure hospital or transfer to a conventional prison (Gostin, 1991).

11.3 Ethical Issues in Coerced Treatment

Some authors reject any form of treatment under coercion for cocaine or any other form of drug dependence. Szasz (1985), for example, denies that drug dependence exists, arguing that all drug use is voluntary. According to him, the law should not prohibit adults from using any drug, and any drug user who commits a criminal offence should be punished, with drug dependence not being an excuse or an extenuating factor. The punitive consequences of this form of libertarianism enjoy more public or political support than any implications it has for the legal status of drugs.

Others, such as Newman (1974), accept that drug dependence exists but oppose compulsory drug treatment on the grounds that it is ineffective. If treatment under coercion is ineffective, then there would be no ethical justification for providing it. Of course, even if treatment under coercion is effective, it does not necessarily follow that it should be provided. The community may, for example, place a higher value on punishing than rehabilitating drug offenders (Hall, 1997).

American evidence suggests that treatment for heroin dependence, such as, methadone maintenance, therapeutic communities and drug free counselling, is of benefit to those who receive it (Gerstein and Harwood, 1990; Hubbard et al, 1989). But the benefits for any individual are still uncertain since treatment assists a bare majority of those who receive it (Gerstein and Harwood, 1990), and relapse to heroin use after treatment is high. The treatment of cocaine dependence is much less effective than treatment for opioid dependence (Kreek, 1997; Platt, 1997). This weakens the ethical justification for "civil commitment" for cocaine dependence but it does not rule out less coercive forms of treatment.

A consensus view on treatment under coercion prepared for the World Health Organization (Porter, Arif and Curran, 1986) concluded that compulsory treatment

was legally and ethically justified only if (1) the rights of the individuals were protected by "due process", and (2) if 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 over-crowding.

The uncertain benefits of coerced treatment have led some proponents to argue that offenders should be allowed two "constrained choices" (Fox, 1992). The first constrained choice would be whether they participate in drug treatment or not. If they declined to be treated, they would be dealt with by the criminal justice system in the same way as anyone charged with their offence. The second constrained choice would be given to those who agreed to participate in drug treatment: this would be a choice of the type of treatment that they received. There is some empirical support for these recommendations in that there is better evidence for the effectiveness of coerced treatment that requires some "voluntary interest" by the offender (Gerstein and Harwood, 1990).

11.4 Conclusions on Coerced treatment

The most ethically defensible form of legally coerced treatment for drug dependent offenders is the use of imprisonment as an incentive for treatment entry, and fear of return to prison as a reason for complying with drug treatment. Offenders should have a constrained choice as to whether they take up treatment or not, and, if they choose to do so, they should be able to choose from of a range of treatment options.

If a cocaine vaccine is used under legal coercion, its safety, effectiveness and cost-effectiveness should be rigorously evaluated (National Research Council, 2001) to ensure due process is observed and effective and humane treatment is provided to cocaine dependent offenders. We also need to be realistic about what these programs can deliver. They are not a panacea for drug-related crime, or prison over-crowding but it may improve the poor record of incarceration (Gerstein and Harwood, 1990). With these modest expectations and with these safeguards, the use of PCBAs under legal coercion may have a *limited* role as one of a range of treatment options. Any such use should be done cautiously and after considerable experience has been acquired in its therapeutic use with voluntary patients.

12. Preventive Uses of a Cocaine Vaccine

If a cocaine vaccine is safe and effective in treating cocaine dependent persons, some will no doubt argue that it should be used to prevent cocaine dependence in adolescents and young adults. Such a possibility is speculative but it has been raised (Cohen, 1997; 2000) and it is a potential use of a cocaine vaccine that, in our experience, is often in the forefront of public discussions of such a vaccine. We accordingly briefly discuss it.

The preventive use of a cocaine vaccine would be arguably ethical in adults who voluntarily decided to use them after being informed of the risks. The vaccine would need to be shown to be safe and effective for this purpose, with higher standards of proof generally required for the safety and efficacy of preventive measures. The foreseeable risks of using the vaccine would have to be communicated to the person, who would have given informed consent to its use, and steps would need to be taken to protect the person's privacy. Under these conditions, the voluntary administration of a cocaine vaccine to a consenting adult who adjudged themselves to be susceptible to cocaine dependence would be ethically acceptable. This scenario is likely to be uncommon so we foresee that such use is likely to be very rare.

The preventative vaccination of children and adolescents against cocaine dependence is an ethically complex issue. Children would presumably be immunized against cocaine dependence at the request of their parents who would consent on behalf of their children who, as minors, would not be legally able to give informed consent on their own behalf. Parents already make a wide range of choices on behalf of their children that affect their lives as adults (e.g. their neighbourhood, diet and education). Some argue, therefore, that immunization against cocaine dependence would be simply another decision that some parents would make for their children (Cohen, 1997). On this argument, a parent would have the right to immunize their child against cocaine dependence in much the same way as they have the right to vaccinate a child against measles or infectious disease (Kaebnick, 2000).

Cocaine use may start in adolescence. Adolescents under the age of majority are able to reason and have sufficient capacity to be involved in decisions about their future, such as, whether they want to be immunized against cocaine dependence. Even if it is ethically acceptable for parents to consent on behalf of their children, the assent of an adolescent or an older child should be sought. Their failure to give assent should only rarely be over-ridden and probably only if there is a morally strong reason for doing so (a case for which could be made to the satisfaction of an independent body, such as, a court).

On the limited evidence or clinical experience with a cocaine vaccine we believe that there it is too early to consider using a vaccine to prevent cocaine dependence in adolescents. This does not mean that such a policy is unethical; only that it should not be implemented without much more careful ethical analysis and community debate. And this should only occur after considerable experience with its use with consenting adults.

13. Conclusions

1. Cocaine dependence is a serious personal and public health issue in some developed countries and is becoming one in some developing countries. Cocaine dependence is difficult to treat because of the absence of effective psychosocial or pharmacological treatments.

2. A cocaine vaccine and other PCBAs have a number of potential advantages over existing treatments, namely, they block cocaine from entering the brain, they may have fewer side effects, and they are likely to have better rates of patient compliance because they are administered less often than oral drugs.

3. The evidence of their effectiveness is confined to studies using animal models of cocaine dependence. These results, and the results of one phase 1 clinical trial, are sufficiently promising to warrant human trials of efficacy.

4. Human clinical trials of the efficacy and safety of a cocaine vaccine will need to address the standard ethical issues of informed consent and rigorous trial design.

5. If a cocaine vaccine proves effective in human clinical trials, the least ethically problematic use will be using cocaine antibodies to manage cocaine toxicity and overdose.

6. A cocaine vaccine will not be a stand alone treatment for cocaine dependence. When used in the context of good psychosocial care it may improve abstinence rates but it is unlikely to be 100% effective. It will not completely block the effects of smoked or injected cocaine and patients will be able to over-ride its effects by increasing the dose of cocaine or by using other stimulant drugs. The effectiveness of a vaccine may be improved by using it in combination with other PCBAs and with other pharmacotherapies for cocaine dependence.

7. The use of a cocaine vaccine to treat cocaine dependent persons will be ethically acceptable when used in voluntary patients who have given free and informed consent to their use. This may involve using a cocaine vaccine for passive immunisation with antibodies in abstinent formerly cocaine dependent persons to reduce relapse to cocaine use. The major ethical issues are ensuring free and informed consent to treatment.

8. A possible ethical issue in using a cocaine vaccine will be protecting patient privacy and preventing discrimination on the basis of a cocaine antibody in their blood. This problem is not wholly new: similar issues have been addressed in methadone maintenance treatment for heroin dependence and with HIV seropositivity in injecting drug users. Similar legislative and public education approaches may minimise these problems with a vaccine. The severity of the problem may also be reduced by using “passive” immunisation with monoclonal cocaine antibodies that disappear from the body.

9. The use of a cocaine vaccine to treat legally coerced clients poses more ethical problems. It is arguably ethical to do so if offenders are offered constrained

choices of (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 clinical experience with its use with voluntary patients. Any use of a cocaine vaccine in patients under legal coercion should be on a trial basis with rigorous evaluation of its safety, effectiveness and cost-effectiveness. The evaluation would also need to examine any adverse social or ethical consequences that it may have before it was more widely implemented.

10. The preventive use of a cocaine vaccine is even more speculative and ethically contentious. Any trials of its preventive use should be preceded by extensive clinical experience with a vaccine in voluntary patients who are cocaine dependent. A higher standard of safety would be required if it was used preventively and important ethical issues would be raised, such as, consent to its use by minors, the protection of privacy, and the prevention of discrimination.

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