



Experts Committee on Ethical issues and Professional standards: introduction to the work of the Committee

The Experts Committee on ethical issues and professional standards' mission and objectives are to undertake reflections and to devise opinions in addressing ethical and professional issues in specific drugs and drug abuse-related areas.

In line with the other Group's platforms, it is made up with experts from various professional fields and delegated by member States. Its work is done under the Group's programme of activities adopted for a three-years period during a Ministerial Conference.

The majority of this work is considered as experts' opinions and positions on given subjects and, as such, to be used by decision makers, where appropriate, when drawing up national policies. They are submitted to Permanent Correspondents during their regular meetings but are not meant to be formally adopted or to become formal recommendations to the member states.

The work on « Ethical questions raised by immunotherapy of addiction – the example of the « vaccine » against cocaine », realised between October 2008 and June 2010, were concluded by a Committee's Opinion. It was published together with its appendices and presented during the Ministerial Conference of November 2010.

This publication is also available on the Pompidou Group's website
http://www.coe.int/t/dg3/pompidou/Activities/ethics_en.asp

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OPINION ON ETHICAL QUESTIONS RAISED BY IMMUNOTHERAPY OF ADDICTION -

THE EXAMPLE OF THE “VACCINE” AGAINST COCAINE

Committee on Ethical issues and Professional standards, June 2010

Introduction

Commenced in the United States in the early 1990s, research conducted on laboratory animals yielded a 1996 publication by Barbara Fox¹ demonstrating that only a small part of the cocaine administered to mice “vaccinated” beforehand against this drug reached their brains. Thereafter, Thomas R. Kosten carried out phase 0, I and II clinical trials in Houston on consumers of cocaine, all methadone-stabilised heroin addicts. Of the 115 volunteers, 38% had reduced or halted their consumption of cocaine thanks to the “vaccine”². A similar study is proceeding in Spain, this time on non-heroin dependent cocaine addicts, but its results are not yet disclosed. Trials in phase III are also under way in the United States on other addictions (specially nicotine)³.

The European press has responded to the findings of this American research chiefly by raising questions as to the effectiveness of the vaccine, without being overly concerned about the ethical implications of administering it. In Appendix A hereafter, the expert Committee on Ethical issues and Professional standards conducted an analysis of a selection of such articles and also itemised the issues raised.

In Appendix A, it also singled out “The ethical issues raised by the “vaccines” against certain drugs” and examined the ethical aspects linked with “informed and conscious consent in medical research involving drug dependent persons and drug users”.

The Committee met on three occasions (in Cavtat, Croatia, on 3 October 2008; in Paris on 21 and 22 October 2009; in Paris on 23 and 24 March 2010) to discuss the ethical issues linked with cocaine “vaccine” research and possible marketing, and gave its verdict on this Opinion at its meeting of 22-23 June 2010 in Paris. It recalls that the development of abusive consumption of psychotropic substances is to be understood in a given biological, psychological and social context and that, neuro-physiological research alone will not allow the phenomenon to be curbed, notwithstanding its incontestable value.

1 Business Wire, « ImmuLogic awarded SBIR grant to develop cocaine vaccine », 02.08.1996.- FoxNature, Barbara S., « Efficacy of a therapeutic cocaine vaccine in rodent models », *Medicine* 2, 1996, p. 1129 – 1132.

2 Thomas R. Kosten MD et al., « Cocaine Vaccine for the Treatment of Cocaine Dependence Methadone-Maintained Patients », *Arch Gen Psychiatry*. 2009, 66(10), p. 1116-1123.

3 According to NIDA (National Institute on drug addiction), a clinical trial in the United States (currently in phase III) on « vaccines » against nicotine, is showing promising results. Research on « vaccines » against other forms of addiction, such as addiction to heroin is also proceeding.

Definition

Before any further reflection, the Expert Committee notes a distinction between a cocaine “vaccine” and the commonly understood properties of a vaccine. The World Health Organisation defines a vaccine as: “any preparation intended to produce immunity to a disease by stimulating the production of antibodies. Vaccines include, for example, suspensions of killed or attenuated microorganisms, or products or derivatives of microorganisms. The most common method of administering vaccines is by injection, but some are given by mouth or nasal spray.”

While a cocaine “vaccine” works by mobilising the immune system to reduce the level of cocaine freely circulating in the blood following consumption of the drug, it does not “produce immunity to a disease”.

Cocaine “vaccine” prevents a cocaine consumer from deriving enjoyment from the substance, as the drug wholly or partially fails to reach the brain. The action of the said “vaccine” is relatively short-term (some months) and booster shots are needed to maintain effective levels of antibody in the blood.

Ethical consideration

The media tendency to hold up a vaccine as a miracle cure for cocaine addiction, risks breeding false hopes, as it ignores certain self-evident biological and physiological facts.

It seems obvious that many actors, such as those who develop the “vaccine” and may produce it (researchers, pharmaceutical industry...) or those who may promote it (judicial and health authorities, doctors, politicians...) have an interest in presenting it as a response to all problems.

A vaccine will thus not have a direct effect on reducing the craving for cocaine by a user. If a user is unable to resist these cravings and seeks their normal stimulant effect, the user may seek to increase his/her consumption of cocaine in an effort to counteract the antibody or to use amphetamines, other stimulants or alcohol. And if a user succeeds to stop consumption of all stimulants, he/her will not resolve their underlying personal problems, which are probably at the origin of the consumption. The role, if any, of a vaccine in the treatment of drug misuse is as yet therefore undetermined. And were a role to be identified, it would be important that its use was governed by the ethical principles governing personal autonomy.

Recognised by Article 8 of the Convention for the Protection of Human Rights and Fundamental Freedoms, the right to privacy and thus to the choices that follow from it, may nevertheless be restricted by the public authority’s possible interference with the exercise of this right when such interference is prescribed by law and necessary for upholding law and order, preventing criminal offences and protecting health, morals or the rights and freedoms of others.

It is possible that a judicial body could be tempted to induce an offender to accept the cocaine “vaccine” in order to prevent further consumption. This could be because cocaine consumption was itself prohibited or because an unlawful act was committed related to consumption. As shown above, this measure is unlikely to be effective. Moreover, it has not been demonstrated yet that a “vaccination” will never have any negative effects on the bio-neuro-physiological system of an individual.

Great care would also be needed to ensure that valid informed consent had been given by the adult to whom the vaccine would be administered to, whether or not they were an offender. The same would apply were the “vaccine” was to be administered to a minor whose parents would have given their consent.

In any case, preventive administration of the “vaccine, even to consenting adults, can never be justified from an ethical point of view. It is also true that, routine preventive administration of the “vaccine” to children or adolescents analogous to immunisation against childhood illnesses could not be justified.

Conclusion

The expected availability of immunological treatments for dependency on certain drugs opens up interesting prospects in terms of treatment, whose implications have not yet been sufficiently explored and weighed up. The term “vaccine” is unfortunate and leads to a misunderstanding of the mechanisms at work, and hence to ill-founded expectations. Real neurological effectiveness is limited indeed and less automatic than in the case of infectious diseases, which provide us with the model. It must at all events be integrated into the psychological and social context of the person under treatment.

Great vigilance is necessary when the privacy and freedom of these individuals are at stake, who risk to be submitted to strong pressure in order to accept the administration of a “vaccine”. Special attention should also be granted to the possibility of change in the psychological state of the person under treatment by the regular administration of such a “vaccine”.

The attitudes and actions of various bodies which may claim welfare or public interest motives in order to further their own interests should also be examined carefully.

Preventive administration of the “vaccine” should in no way be envisaged.

The expert Committee on Ethical issues and Professional standards calls to regard the immunotherapy treatments of addiction with the greatest caution : It warns against excessive and unfounded expectations and possible adverse effects. It considers that in case such “vaccines” are to be put on the market, very strict application frameworks should be implemented to prevent the risk getting out of control.

THE ETHICAL ISSUES RAISED BY “VACCINES” AGAINST CERTAIN DRUGS -

SUMMARY OF THE COMMITTEE'S REFLECTION

Committee on Ethical issues and Professional standards, June 2010

Introduction

1. One of the means of preventing or treating drug addiction currently being investigated consists in modifying human beings' receptiveness to given substances. This is what is known as "immunological treatment", or more colloquially "vaccination". The research on laboratory animals started in the United States in the early 1990s led in 1996 to a publication by Barbara Fox showing that only a small portion of the cocaine administered to mice previously "vaccinated" against this substance actually reached their brains¹. Subsequently, phase 0, I and II clinical trials were conducted by Thomas R. Kosten in Houston on cocaine users, all of whom were heroin addicts stabilised by methadone treatment. 38% of the 115 volunteers reduced or ceased their cocaine use thanks to the "vaccine"². A similar study is in progress in Spain, this time on cocaine users not addicted to heroin, but the findings have not yet been disclosed. This work primarily concerns cocaine, but other possibilities are emerging (amphetamines, nicotine, etc.)³
2. Although this work has not yet yielded any operational results, the prospect is already arousing considerable interest:
 - A search for the two words "vaccine" and "cocaine" on the Internet gives 1.3 million hits
 - At the same time, the press has already reported these findings, with reference mainly to the issue of the effectiveness of the vaccine, while barely mentioning the ethical implications of its use (See the analysis of a selection of press articles - P-PG/Ethics(2010)9 – enclosed as appendix 2)

1 Business Wire, « ImmuLogic awarded SBIR grant to develop cocaine vaccine », 02.08.1996.-
FoxNa ture, Barbara S., « Efficacy of a therapeutic cocaine vaccine in rodent models », *Medicine* 2,
1996, p. 1129 – 1132.

2 Thomas R. Kosten MD et al., « Cocaine Vaccine for the Treatment of Cocaine Dependence in
Methadone-Maintained Patients », *Arch Gen Psychiatry*. 2009, 66(10), p. 1116-1123.

3 According to NIDA (National Institute on drug addiction), a clinical trial in the United States (currently
in phase III) on « vaccines » against nicotine, is showing promising results, but one of the problems
encountered concerns the antigenicity of adjuvants, which are too weak to initiate a sufficient im-
mune reaction. Research on « vaccines » against other forms of addiction, such as addiction to
heroin is also proceeding

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The Ethical issues raised by „vaccines“ against certain drugs: summary of the Committee's reflection

3. A study of this media output reveals some problematical aspects:
 - A big discrepancy can already be noted between the state of the research and the perception the public and politicians have of this discovery. It would therefore be necessary to work on these perceptions before recommending applications;
 - The solution's potential implementation has many ethical implications. To our knowledge, no recommendations have yet been made by national ethics committees;
 - The difficulties are linked in particular to the huge lack of knowledge about the complexities of the human organism and of society.
 - There is accordingly a need for an in-depth debate.
4. The role of ethics is to stimulate discussion that takes account of the different aspects and the positions of the various parties involved. The solutions adopted or recommended are thus less likely to meet with hostility from parties who consider that their viewpoint has been ignored, and this offers better guarantees for their implementation. This discussion, held outside the political sphere and hence free from political tension, nevertheless paves the way for policymaking insofar as its success is based on public support and hence on proper consideration of the different approaches.
5. Following a joint meeting with the expert Committee on Research (Cavtat, 1 and 2 October 2008), the Pompidou Group's expert Committee on Ethical issues and Professional standards decided to address the ethical issues which this research and its potential applications may raise. This report is the outcome of exchanges between the members of the Committee at four meetings: 25-26 March 2009, 21-22 October 2009, 23-24 March 2010 and 22-23 June 2010. The main conclusions are set out in an Opinion published along with this appendix.
6. The specific example of immunotherapy of addiction will doubtless make it possible to highlight a number of risks and to issue wider-ranging recommendations. Choosing this theme at a time when the possibilities opened up by the research findings are still far from being exploited in practice enables the Committee to discuss the issues before any policy decisions are taken and should help its conclusions find a ready ear.
7. The ethical issues raised by the "vaccines" in question are of different kinds:
 - a. The situation of participants in the trials is no different from that of the "guinea pigs" used in any other research project in terms of the risks incurred, the information requirements, consent and so on.;
 - b. Questions must be asked firstly about the impact of administering the immunological treatment ("vaccine") as regards its effectiveness and any adverse effects and, secondly, about consent by the persons concerned and whether there are legitimate grounds for possibly coercing them into treatment (see Part II below).
 - c. The development of these treatments generates expectations and reactions among different social players: the general public, treatment manufacturers, health care practitioners, the authorities, etc (see Part III below).

8. It should be emphasised from the outset that the term “vaccination” is misleading. As will be seen (Part I below), it does not refer to the mechanisms usually denoted by this term in medicine. It might therefore lead one to believe that there are automatic effects and raise false expectations, leading to actions that are ineffective or which might even pose a threat to the personal integrity of individuals. This might also give rise to actions by different players that depart from the, in principle, commendable objectives pursued. Nevertheless, these possible departures would not justify abandoning the research in question. They do, however, call for the interpretation and possible application of the results.

I – Characteristics of an anti-drug “vaccine”⁴

9. Although an individual's psyche and social profile play an important role in drug consumption and dependence, it is true that the substances concerned are active in so far as they change neurological functioning. Research in the neurosciences can therefore make a significant contribution to understanding the phenomenon and perhaps treating it. The pain and reward circuits are affected in particular, and the researchers are seeking to identify the neurotransmitters involved, the location of their receptors and the molecules that make it possible to mimic or block them.
10. We are now capable of intervening against neurological dysfunctions: this can be seen, for instance, with the use made of electrical stimulation in treating Parkinson's disease and perhaps soon other brain malfunctions (epilepsy, obsessive compulsive disorders and so on). It is therefore not unreasonable to wish to regulate sensitivity to certain products. However, the neurological problems which we are beginning to treat in this way are principally somatic diseases. In drug dependence there are significant psychological and behavioural factors at play, and neurological action proper is only one aspect of the phenomenon. It is reasonable to believe that so-called immunological treatment will become part of the range of responses - not immediately but within a few years or decades - but it must not be credited with a key therapeutic capacity. Regarding it as a panacea would be a technical mistake and, hence, ethically wrong.
11. The nervous system's sensitivity to the substances in question varies from one individual to another. Differences can be found on three levels: a) genetic influences (hereditary), b) personal development (epigenetic factors), c) experience, that is to say prior consumption history. Sensitivity therefore varies and is either innate or acquired.
12. The aim of immunological treatment would be either to counter a genetic or epigenetic predisposition so as to reduce the impact of the substance concerned and prevent dependence taking hold at stage c) or, in a way, to alter the experience acquired at stage c), that is to say the addiction, so the subject reverts to a non addicted stage. The term used here is “pharmacological psychosurgery”⁵. The idea is to change the configuration of the nerve cells' communication system by for example changing the properties of surface receptors or even to modify genes or at least their expression. However, this field of research is still very far away from offering treatments.

4 This section drafted by the Ethics Committee has been reviewed and amended by Pr R Muscat, Co-ordinator of the Research Committee.

5 Pr Springer's paper at the Cavtat Round Table - P-PG(2008)7 available on the Pampidou Group's website www.coe.int/pampidou

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13. The less invasive option currently being explored consists in using the immune system's reactions to counter a drug's effects. Unlike with an infectious disease, the organism's defence mechanisms do not recognise the drug molecule as a foreign agent and do not produce antibodies. Nonetheless, it is possible to administer a molecule (protein) to which one or - usually - more molecules of the drug have been attached. This complex is identified as foreign and stimulates the production of antibodies. When the drug in question subsequently enters the blood stream, it binds to these antibodies. Once it is captured in this way, it is no longer free and, in particular, is prevented from reaching the brain - it's major target. It should however be noted that the new complex formed by the antibodies and the captured drug molecules remains in the blood stream, although it is neurologically inactive, and is eliminated only over a period of some months.
14. The use of the term "vaccine" is understandable, since it is a question of making people resistant to a substance's effects so they no longer crave it. It is nonetheless somewhat improper. In traditional medicine a vaccine uses the normal immune responses to produce antibodies against aggressors (such as bacteria or viruses). These antibodies destroy pathogens or bind with them so the leukocytes can detect and digest them. The invader is eliminated at a stage when it is not yet abundantly present, preventing it from multiplying; the attack will in fact have affected only a small number of the organism's cells (another advantage is that the pathogen is eliminated before it is re-exported, thereby contaminating other organisms). However, in the case under consideration here the biochemical mechanism is different, since the drug does not replicate inside the organism. From the outset the quantity ingested is sufficient to produce the psychic effects the treatment is seeking to prevent. This means that there is a significant quantitative difference: the dose to be neutralised is considerably larger than the small number of viruses or bacteria that have to be killed in the case of a contagious disease. To block the molecules introduced, it is necessary to "consume" a significant share of the antibodies previously produced, and, unlike with an infectious disease, it cannot be taken for granted that a new intake of the drug will generate fresh antibodies. Furthermore, when the antibodies in question are not consumed following a new intake of the drug, it is not known whether they will remain in the body for several years, as is the case with ordinary vaccinations, or whether they will in any case be eliminated in a few months.
15. Vaccination moreover seeks to protect the organism against an undesirable pathogen, which is attacking a passive recipient, whereas, in the case of drug dependence, the substance is often actively sought after by the individual who derives a benefit from it, at least to begin with until addiction takes hold. Clients undergoing this kind of treatment can react in one of two ways: either, seeing that the drug has no effect, they stop taking it or, to make up for the amount of the ingested dose mopped up by the antibodies, they step up their consumption. This would lead to something similar to a "tolerance" mechanism.
16. This being the case, the term "vaccine" is incorrect. It brings to mind an infectious disease, which is a false analogy and may mean that treatment is reduced to merely administering the so-called vaccine and relying on its automatic effects.

II – Ethical issues related to due regard for the Individual

17. A treatment must be envisaged only if the expected benefits outweigh the potential disadvantages. This idea is elaborated below in paragraphs 18 to 23.

18. If a benefit is to be expected it can be assumed that research has shown the treatment to be effective. In particular, the research findings must have identified the cases where it is useful and those where it is ineffective or even unsafe. Since effectiveness is demonstrated statistically on a random sample, it cannot be supposed that the treatment can blindly be given to just anyone. It is also necessary that the health care practitioner offering or administering the treatment should have been able to determine that the treatment is suitable in a given patient's case. In other words, the expertise required to choose an appropriate treatment method must be distinguished from the justification for a political, judicial, health care or other authority to make treatment compulsory.
19. The concept of "benefit" must be clarified. Is it a matter of overcoming dependence or of preventing it? In the latter case will "vaccination" be offered to, or imposed on, non-dependent users, whose consumption currently has no negative effects, with a view to forestalling a possible future dependence? More specifically, the benefits of halting consumption can be ascertained in the light of the reasons why the person is currently using drugs and the potential negative impact thereof. Put in simple terms, there would be three possible scenarios:
 - a. Consumption for recreational purposes or occasional use, which is of no current detriment to the user or to others. Because of the independent status of each individual, it is acknowledged that people are able to engage in such consumption and in such cases the possibility of "vaccination" does not arise.
 - b. Routine consumption to help cope with a personal problem. Whatever the nature and the origin of the problem, drug taking can have compensatory effects and help people deal with difficult situations. Of course, it is regrettable that this is the only way out of their distress they have found. However, any treatment that deprived them of this relief without solving the underlying problem would then trap them in this situation. Whether "vaccination" is recommended by an authority or they ask for it themselves, the effect may be the opposite of the one sought.
 - c. Long-term dependence with adverse effects on health and behaviour. On the face of it, a "vaccination", which would discourage the person from consumption by making it inoperative would appear to be beneficial. It may well be, however, that the imperative need to take drugs remains. So-called "vaccination" works by producing a number of antibodies, which deactivate the substance in question (in this case, cocaine), and it is possible to saturate these antibodies by increasing the amount of the product absorbed. In such circumstances, "vaccination" will not have halted consumption or its adverse effects, only increased the amounts consumed. This possibility arises in cases of confirmed dependence but it can also occur in cases of "craving", which is an irrepressible urge to consume drugs, experienced particularly commonly by cocaine users. Episodes of craving can come about even where the user is not dependent.
20. Further, whose role is it to determine that a treatment is beneficial or not? What does one do about those who are happy with their drug usage or even their dependence? On what basis can a user's entourage or the community impose their definition of harm, whether caused to that user or to society, or conversely determine the benefit that the user concerned or society will derive from stopping the drug usage? In fact, given that the cost of "vaccination" is likely to be high – while funders are already reluctant to support psychological therapies which will in any event remain necessary



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– it would probably be limited to confirmed drug addicts (tertiary prevention). And it should be reiterated in this connection that, with the current state of technology, the immunity obtained through “vaccination” lasts only a few months, meaning that the treatment needs to be renewed relatively frequently.

21. One possible “adverse effect” is that the treatment will induce the opposite effect from that desired. This is a rare occurrence in medication-based somatic medicine but does sometimes happen: with traditional vaccines there have been some cases where the pathogen extract was insufficiently inactivated and caused the very disease it was supposed to protect against. Clinical trials seek to prevent this and, in some cases, incidents have led to the withdrawal of a treatment's licence. In the field with which we are concerned here, where the client's behaviour is a key factor, it may be (as mentioned in § 19 above) that, having been freed of an addiction but not of the psychological or social distress which originally caused it, clients will increase their consumption. Otherwise, they may switch to another drug such as amphetamines or alcohol. In other words, the question is what is being cured: addiction to a specific substance, the dependence itself regardless of the substance concerned or the problem (dissatisfaction, angst, mental illness, living conditions, and so on) that caused the drug dependence in the first place?
22. A second type of adverse effect occurs outside the area being treated. The term “side effects” is often used here. With traditional vaccines attention is paid to these complications, which are often mild and of short duration (postvaccinal reactions, skin rashes, a high temperature, etc.). However, sometimes the person concerned develops another disease. Some years ago there was a controversy surrounding the possibility that hepatitis B vaccination might be associated with the onset of multiple sclerosis. Since the research findings were inconclusive, the public authorities decided to no longer recommend vaccination. It is also a known fact that the immunodepressors particularly suited to treating certain serious diseases involve a risk of “opportunistic” infections. Such unplanned, undesirable effects can be noted in somatic medicine, where the processes are nonetheless more deterministic. In mental health care, things are unquestionably even less predictable. Without even talking about the destructive treatments (surgical or chemical) which cure patients but deaden their minds, great caution must be exercised regarding the unforeseeable, indirect effects that a modification of mental and therefore psychological functioning may have. Changing one small thing in an extremely complex system can have unexpected dramatic consequences. This uncertainty is of course not a reason for abandoning all attempts to change the situation, but extreme prudence regarding the possibility of triggering serious side effects is nonetheless called for.
23. The preceding paragraphs investigate whether the effects of immunological treatment (or “vaccination”) are those that are expected. While these methods are unquestionably one way of achieving these effects, it is clear that they are unpredictable because they depend on a varied range of circumstances. This being so, the question is whether to proceed with such “vaccination” or not. Even if clients ask for it, it is no doubt essential to ensure that they do not harbour any hopes based on incomplete information. This is all the more important where the decision is taken on clients' behalves, and their entourage or a medical judicial or hierarchical authority proposes, or even imposes, such treatment. In the course of examining the possible effects, the preceding paragraphs frequently touched on these questions without dealing with them explicitly. However, it is a crucial ethical issue to decide

who can recommend or require the treatment in question, and for what purpose and with what degree of certainty.

24. Clients' consent to treatment is central to their human condition. The ethical rules that govern our societies, as set out in the Declaration of Human Rights, require that respect be shown for the individual's personality. This is both a moral principle which enshrines the concept of human dignity and a governance principle whereby, in a democracy, society cannot tyrannically oppress individuals. However, that does not diminish the individual's responsibility towards society in any way. It is indeed an element of the individual's dignity as a member of society that he or she should not impose his or her egoism and whims on others. A balance must therefore be struck between individual autonomy and the duty not to harm society. It is on this ground that vaccination against contagious diseases can be made compulsory. Designating a treatment aimed at reducing sensitivity to cocaine as a "vaccine" gives the impression that it is a matter of combating an infectious disease, which would be a justification for imposing an obligation. As mentioned above (see section I), this comparison is conceptually incorrect: then any prophylactic treatment copying the case of medicine would be problematic. If there is contagion, it is not that caused by a pathogen passed on from one person to another, but takes the form of infectious behaviour: in this case the "disease" is spread by means that have little to do with biology but are primarily psycho-relational. If the intention were to make treatment compulsory, the justifications for the obligation would have to be founded on social disruptions other than contagion.
25. Furthermore, if a "vaccine" of this kind were available, consideration would have to be given to the question of its accessibility to those wishing to benefit from it and, alternatively, in the event of treatment being compulsory, the question of who decides that this is appropriate and on the basis of what information. (see, in § 28 c below, potential stigmatisation in the workplace.) In all cases, it would be necessary to determine who must bear the cost.
26. Assuming that a so-called "vaccine" is available and action is taken to counter the risks of undesirable effects, the fact remains that the intention is to modify neurological and psychological functioning, which also shape the client's personality. The respect that must be shown for the latter, even where this personality is deemed to be disordered and to deviate from the "norm", precludes administering treatment without the client's consent. This prohibition could be overridden only if the client were blatantly suffering from mental alienation. This means that two precautions must be taken:
 - firstly, it must be possible to determine a limit beyond which consent could be dispensed with;
 - secondly, where this limit is not reached the client must be involved in the treatment decision by being honestly informed of what it entails and by being asked to give genuine consent.
27. In certain cases, such as addiction to nicotine, where discernment is not impaired, the client more easily consents and is sometimes even seeking treatment. However, in other cases drug dependence itself affects the client's mental awareness and judgment, making it hard to assess the true nature of consent. The question is even more delicate if it is borne in mind that, in cocaine or heroin addiction, for example, awareness is not permanently impaired and there are moments of lucidity.



Furthermore, consent may be influenced by the prevailing opinion or by advertising (example of the “denormalisation” of smoking): although this may be desirable, it nevertheless raises the issue of what constitutes consent and how solid it is. Clearly, consent also has to be understood as being fully informed, particularly as regards the expected benefits, their likelihood and also any possible side-effects, like the risk of increasing weight for a person who stops smoking.

III – Ethical problems posed by interaction between the players concerned

28. The prospect of availability of a treatment - especially where it is called a vaccine, thereby implying that protection will be automatic – gives rise to different kinds of hopes in the players concerned:

- a. Those who are sufferers, or consider themselves as such, see themselves already cured. It is unethical to allow them to sustain their hopes when the treatment in question is still uncertain and distant;
- b. Public or private authorities wishing to reduce drug dependence believe they have a solution to the problem and are tempted to promote or even impose it. It must be ensured that they take fully into account the technical and ethical conditions for the use of this treatment. They may sometimes perceive it as a solution that is sufficient in itself and requires no further action; We would also need to see who would pay for these “vaccinations”: does the obligation mean that governments should cover the cost? Otherwise, some drug addicts do not have much money and even if need drives them to find money for their drug, there is no certainty that they would find the money to free themselves from their addiction;
- c. Employers who could be tempted to test for the presence of vaccine antibodies, leading to stigmatisation or even exclusion of the persons concerned. Or conversely, they might make a former drug addict's continued employment conditional on proof that he or she carries the antibodies in question. Reference is made here to the opinion given by the Ethics Platform on drug testing in the workplace [P-PG/Ethics(2008)5];
- d. The treatment manufacturers see a lucrative market in the offing and lobby both practitioners and policy-makers to develop use of the treatment;
- e. Researchers, captivated by their own technical skills and the enhanced reputation and funding they can derive from such a discovery, are tempted - albeit not all of them - to go along with the expectations of the public, the authorities and manufacturers by fostering the belief that the solution they have found is effective in itself, without the above-mentioned restrictions, precautions and attendant considerations. It is of course necessary not to hamper research, but it must be borne in mind that the results must not be interpreted in such a way that more is read into the findings than exists;

These various players are tempted to stir up popular support for their narrow viewpoints by advancing grounds of public health or public order and demagogically popularising over-simplistic ideas on the subject which they then turn into arguments for taking actions consistent with their own interests.

29. The objectives pursued here are very comprehensible and often justifiable. However, the high stakes involved push all the players to exploit whatever seems to be a means of serving their own aims. There is a temptation in particular to treat the

research results as a mere means to an end. Care must therefore be taken not to nourish unrealistic expectations compared with the real possibilities offered by this kind of treatment. Drawing attention to this pitfall does not amount to denigrating the various parties' motives.

Although there is every reason to support the research in question – while ensuring, as mentioned above, that parallel work is carried out in other fields and disciplines, given the multifactorial nature of drug dependence – the direction taken by the research may raise issues, such as the independence enjoyed by researchers in deciding their programmes, the extent to which they should be guided by public policy, and on the basis of what criteria, and the extent to which the direction of research is influenced by public funding or funding by pharmaceutical laboratories.

30. These different parties accordingly have objective interests which can cause them to rush headlong into giving these treatments their unquestioning support. However, their interests, albeit diverse, can be mutually reinforcing. This then creates a vicious circle of misrepresentation and misuse which is difficult to break. A key ethical requirement will therefore be that everyone should be wary of their own impulsive reactions and of those of others. This therefore brings into play each profession's - researchers, doctors, journalists, politicians, civil servants, business owners and managers, counsellors - own code of ethics.⁶
31. It is also possible that difficulties may arise from the way their spheres of action overlap and impinge on one another, without any party being responsible for the problem. A joint effort must therefore also be made to overcome systemic bottlenecks and to avoid being carried away by the general enthusiasm.
32. The above comments do not solely concern immunological treatment of drug dependence. The same temptations to oversimplify and the same interplay between the parties concerned should also be borne in mind when addressing the issues of drug testing, substitution or quasi-coerced treatment, for example.

Conclusion

33. The expected availability of immunological treatments for dependency on certain drugs opens up prospects, the implications of which have not yet been sufficiently explored and weighed up. The term “vaccine” is unfortunate and leads to a misunderstanding of the mechanisms at work, and hence to ill-founded expectations and perhaps inappropriate applications. Real neurological effectiveness is limited, however, and less automatic than in the case of infectious diseases, which provide us with a model.
34. A first category of ethical issues concerns the individual and calls for great vigilance. His or her privacy and freedom are at stake, and these may only be infringed on specific grounds. A further question concerns the possibility of personality change, even though drug dependency itself already involves an alteration of personality.
35. A second category of issues concerns the attitudes and actions of various bodies – often in conflict but also able to form opportunistic alliances – which may claim welfare or public interest motives in order to further their own interests. Whatever solutions are proposed, these interactions also call for vigilance.

⁶ Professional standards are what govern relations between a profession and the rest of society.

ETHICAL QUESTIONS RAISED BY IMMUNOTHERAPY OF ADDICTION -

ANALYSIS OF A SELECTION OF ARTICLES PUBLISHED IN THE EUROPEAN PRESS

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1. Introduction

Neurobiological research provides valuable information on behavioural and cognitive problems associated with addictive conducts linked to the taking of psychoactive substances. Various types of long-term treatment geared to blocking the effect of the substances on the body, particularly immunotherapeutic procedures, stand out among the new ideas being explored in pharmacotherapy for addictions. Such treatment differs from the rest in terms of the duration of its action and the mechanism involved. Unlike most existing types of treatment, which act on the brain, the immunotherapeutic approach blocks the drug in the blood upstream of the central nervous system, which improves user tolerance. According to a group of experts mandated in 2004 by the National Institute of Drug Abuse¹, however, the approach has the following limits: 1) such treatment can only be used on specified groups of patients in relation to highly specific psychoactive substances; 2) the short-term irreversibility of this therapeutic choice necessitates a high degree of prior motivation; 3) some users might be concerned about traces of the treatment in the body which remain detectable in the long term; 4) other users might be induced to take substances other than the one being targeted; 5) the perception of supposedly highly effective types of treatment might lead to complacency; 6) illegal drug markets are also liable to alter their supplies.

The risk of disproportionate public expectations is intensified by the widespread use of the word “vaccine” to refer to these new therapies. From the immunological point of view, “vaccine” refers to the process of triggering an immune reaction in the body with a view to inactivating the effects of a pathogenic agent, which may or may not be infectious. In common parlance, however, the word “vaccine” is assimilated to the treatment and prevention of infectious diseases.

This document is intended to provide information on ethical issues relating to addiction immunotherapy which are brought to the public attention. We accordingly conducted a review of the scientific press, followed by an analysis of a selection of articles published in the general press in Switzerland and a selection of our European countries.

2. The state of research in immunotherapy for addictions

2.1 Principle of the “anti-addiction vaccine”

Two different forms of immunisation are capable of being developed in order to block the effects of a psychoactive substance².

Passive immunisation consists in injecting into the body monoclonal antibodies obtained through genetic engineering. This procedure might be envisaged for treating overdoses and preventing relapses in the short term in persons being treated with a view to total abstinence.

Unsolved technical problems relate to controlling the life span of the antibodies injected, which is either too long, in the case of treatment for overdoses, or too short, for preventing relapses.

Active immunisation involves repeated injections of a so-called “Hapten-Antigen” complex. The psychoactive substances involved in these techniques are too small to trigger an immune response unless they are combined with a large molecule capable of conferring the desired immunogenicity. The aim is to obtain sufficiently high concentrations of endogenous antibodies, whence the need for repeated injections (unlike anti-infection vaccination, where there is no need to maintain a concentration of circulating antibodies, as the lymphocytes are capable of reactivating the manufacture of antibodies sufficiently quickly in the event of re-exposure). The main technical problems encountered here concern high inter-individual variability of immune responses and the three- to six-week action period.

In all cases it is possible to “force the immune barrier” by increasing the dose of the psychoactive substance targeted by the antibody.

2.2 State of research

Studies have been carried out on animals for Phencyclidine (PCP), Methamphetamine, heroin and morphine, nicotine and cocaine. These studies have shown the efficacy of the immunisation obtained in terms of concentration of the substance in the brain, locomotive effects of the substance and self-administration³.

“Phase I” (study of tolerance in healthy subjects) and “Phase II” (pilot studies of efficacy in a small number of patients) clinical studies have been conducted with nicotine and cocaine. Phase III studies (studies of efficacy with a control group) should be conducted and published in the near future⁴.

2.3 Historical background to the “anti-cocaine vaccine”

Research into “vaccines” against cocaine began in the United States at the beginning of the 1990s with testing on animals by researchers from the ImmuLogic pharmaceutical laboratory, which financed the research, and their colleagues at Boston University⁵. After the success of these tests on animals, the British pharmaceutical laboratory Xenova produced the TA-CD vaccine, which was subsequently tested on human beings by Professor Thomas Kosten and his team at the Yale School of Medicine, with the support of the National Institute on Drug Abuse (NIDA) in the United States.

Phase I and II clinical studies were conducted between 1997 and 2004. In October 2009, Professor Kosten’s team published a report on the Phase IIb clinical tests conducted at the Baylor College of Medicine in Houston. These tests covered a total of 115 cocaine addicts, 58 of whom had received five injections of the vaccine and 57 mere placebo injections. 38% of participants in the “vaccinated” group developed sufficiently high concentration of antibodies to reduce or halt their consumption of cocaine⁶.

In Europe, similar work has apparently been initiated, particularly in Spain, where there were plans in 2009 to conduct testing on 150 volunteers in several specialised centres⁷. We have no knowledge to date of the publication of any final or provisional results.



3. Ethical questions in the field of immunotherapy for addictions

3.1 Data from the scientific literature

A bibliographical search via Medline OVID to identify articles containing the keywords “cocaine”, “addiction”, “dependence” and “vaccine”, filtering the articles identified with the keyword “ethics”, enabled us to select 11 articles published from 1997 onwards⁸.

The articles identified mainly concern the therapeutic approach to cocaine dependence⁹¹⁰¹¹¹²¹³¹⁴¹⁵¹⁶. A minority of the articles deal with the therapeutic approach to nicotine dependence¹⁷¹⁸¹⁹.

The critical arguments present in the articles published in the scientific press concern the following fields, in order of frequency:

- Respect for the private lives of the drug-taking persons: antibodies are detectable in the blood and may indicate that the person has (had) an addiction problem²⁰²¹²²²³.
- Risks of poisoning and overdose: a person who nonetheless wants to take drugs could attempt to obviate the effect of the treatment by consuming massive doses of the product, leading to risks of overdose or poisoning by adulterating agents used in the preparation of illegal drugs²⁴²⁵²⁶²⁷.
- Complexity of defining the concept of freedom in relation to the consumption of substances potentially generating addictive behaviours²⁸²⁹³⁰³¹.
- Specific problems arising from the use of immunotherapy for the purposes of primary prevention³²³³³⁴³⁵.
- Action of the vaccine confined to one substance only³⁶³⁷³⁸.
- General problems relating to assessing the capacity for discernment and consent in the field of treating addictive behaviours³⁹⁴⁰.
- Importance of assessing the indication for immunotherapy in a manner taking account of the individual clinical state⁴¹⁴².
- Partial and reductionist dimension of immunotherapy as a tool which must be integrated into a bio-psycho-social therapeutic approach⁴³⁴⁴.
- Duty of scientists, media and the authorities to provide accurate and exhaustive information on the vaccine⁴⁵⁴⁶.
- Hijacking of vaccine for ideological purposes, especially in promoting an ideology based on the aspiration to a “drug-free society”⁴⁷.
- Inappropriateness of the word “vaccine”⁴⁸.
- Difference between anti-addiction immunotherapy and anti-infection vaccination from the angle of the respective weightings of individual and public interests⁴⁹.
- Risk of encouraging drug-taking via the perception of a “simple and definitive” remedy for addiction⁵⁰.
- Ignorance at this stage of the direct side-effects of the type of immunotherapy developed⁵¹.
- Use as a coerced or quasi-coerced treatment⁵².

3.2 Considerations from the Ethical Platform

The Pompidou Group’s Ethical Platform has initiated a debate on immunotherapy for addictions (see draft report P-PG(2009)2rev by R. Padieu and P. Sansoy). Other questions were raised in addition to the critical arguments put forward in the previous paragraph:

- The difference between a traditional vaccine and the anti-cocaine vaccine from the angle of the activity and role of the patient. None of the articles tackles the

issue of the role of the person who is to be “vaccinated”: the aim of anti-infection vaccination is to neutralise the effect of a pathogenic agent which the person is passively suffering against his or her will. However, the individual plays an active role in seeking out psychoactive substances. This point raises the thorny question of self-determination and personal choice in the addiction field.

- The question of modifications of the neurobiological process potentially caused by the treatment: what other changes or indirect side-effects might result? What are the risks incurred?
- The possibility of adaptations of supplies on the illegal drug market.

All these arguments are summarised in Table 1 (see Appendices).

4. Analysis of a selection of articles published in the general press in Switzerland

4.1 Selection of articles

In order to ascertain how the subject of immunotherapy for addictions has been presented in the general French-speaking Swiss press and home in on any critical arguments concerning this approach, we conducted an analysis of articles dealing with “anti-addiction vaccines”. 45 articles from the Swiss general press (French-speaking region) containing the keywords “vaccine” and “cocaine” or “nicotine” were identified between January 2000 and January 2010 via the LEXYS search engine. After revision, we included 32 articles in our analysis. Only three of these articles deal exclusively with the subject of cocaine; the others concern nicotine, and only one addresses both themes simultaneously.

4.2 Observations

Critical arguments and ethical questions mentioned in the regional general press, in order of frequency:

- The vaccine approach to dependence is reductionist and, if it is to be efficacious, it should be supplemented with more comprehensive provision for the individual, eg with therapeutic support⁵³⁵⁴⁵⁵⁵⁶.
- The terminology used is inappropriate: it would be better to say “immunisation” rather than “vaccination”, since this process does not target an infectious agent⁵⁷⁵⁸⁵⁹.
- There are risks of overdosing if the subject attempts to obviate the effect of the vaccine by taking a “massive” dose of the substance (cocaine)⁶⁰⁶¹.
- There is a risk of trivialisation which might make consumers more blasé about taking cocaine, in view of a perceived “easy” solution to possible dependence⁶²⁶³.
- The vaccine targets one psychoactive substance only, posing the risk of the consumer turning to other substances⁶⁴.
- The results obtained with the anti-nicotine to date “vaccine” seem rather modest⁶⁵.

- Broadly speaking, the general press rarely discusses the ethical questions and issues raised by the vaccine, and does not go into detail on the few which it does mention. Only ten or so articles outline the mode of operation of the anti-cocaine and anti-nicotine “vaccines”, putting forward a number of critical arguments against this new approach. The other 22 articles, published in the economy, finance or stock exchange sections, concentrate on the pharmaceutical firms which hold the “vaccine” patent and on the financial implications for the development of the companies in question or, less often, the state of progress in current research.

5. Analysis of a selection of articles published in the general press of several European countries

5.1 Selection of articles

We conducted research and analysis of media reactions to the vaccines against cocaine in five further European countries, namely the United Kingdom, Germany, Spain, Italy and France. We used the keywords “vaccine” and “cocaine”, omitting the keyword “nicotine”, unlike in the preliminary work conducted with the Swiss press.

A variety of sources were used:

- the search engines of major newspapers and magazines in each country;
- the Google search engine, with a selection of criteria concerning a specific country and language.

A total of 43 articles dealing with this subject were selected.

5.2 Observations

Ethical questions addressed, in order of frequency:

- Eleven articles address the matter of primary prevention, wondering whether it would be appropriate and acceptable to treat children with the “vaccine”⁶⁶⁶⁷⁶⁸⁶⁹⁷⁰⁷¹⁷²⁷³⁷⁴⁷⁵⁷⁶. Most of the articles report that the vaccination is a selective procedure, in order to explain why the TA-CD must be administered repeatedly and cannot yet be used as a long-term preventive measure.
- Eight articles mention the possible direct side-effects, describing them as moderate and not dangerous⁷⁷⁷⁸⁷⁹⁸⁰⁸¹⁸²⁸³⁸⁴.
- Seven articles mention the reductionist aspect of this approach⁸⁵⁸⁶⁸⁷⁸⁸⁸⁹⁹⁰⁹¹.
- Six articles stress that the vaccine targets one substance only⁹²⁹³⁹⁴⁹⁵⁹⁶⁹⁷.
- Six articles state that the effect of the “vaccine” can be neutralised by increased consumption⁹⁸⁹⁹¹⁰⁰¹⁰¹¹⁰²¹⁰³. One article, however (UK), suggests that this exposes the patient to possible risks.
- Three articles address the issue of coerced and quasi-coerced treatment¹⁰⁴¹⁰⁵¹⁰⁶.
- Three articles mentioned indirect side-effects¹⁰⁷¹⁰⁸¹⁰⁹. The authors were concerned with the possibility of the “vaccine” modifying neurobiological functions in an undesirable (or even irreversible) manner.
- Two articles deal with arguments linked to self-determination and the concept of the

drug-taker's choice¹¹⁰¹¹¹.

- Two articles stress the need to assess the immunotherapy indication in a manner varying according to the individual's clinical state¹¹²¹¹³.
- Two articles mention the risk of the vaccine being hijacked for ideological purposes in the name of the aspiration to a "drug-free society"¹¹⁴¹¹⁵.
- One article draws a distinction between immunotherapies and anti-infection vaccines in terms of the patient's active role in seeking out psychoactive substances¹¹⁶.
- One article states that the word "vaccine" is inappropriate¹¹⁷.

6. Summaries of observations and conclusions

Most of the articles published in the general press focus on concise but more or less accurate explanations of the technology underlying the development of immunotherapy. On the other hand, very few articles propose a critical analysis of the definition and use of the word "vaccine" in the addiction therapy context. Where they mention the ethical issues, they only do so in a schematic, incomplete manner. More specifically, arguments concerning the autonomy principle (choice, self-determination, consent, discernment, forced treatment, confidentiality) are virtually non-existent in the general press. A large proportion of the articles published in the general press appear in the stock exchange, financial and economic sections.

A small number of articles in the scientific press mention the reductionism of pharmacotherapeutic approaches to addiction (seven European sources, four Swiss sources and two scientific press sources: 13/84). The possibility of using this approach in primary prevention is only mentioned in terms of the technical difficulties this would raise (injections to be repeated frequently in order to obtain a sufficiently high dose of antibodies), but without addressing the ethical questions which such an indication would pose. One article highlights the difference between anti-addiction and anti-infection immunotherapeutic treatment from the angle of the respective weightings of individual and public interests. One article highlights the difference as regards the passivity of a person who is subject to an infectious agent and the active attitude of an individual who actively seeks to consume a psychoactive substance. None of the articles mentions the capacities of adaptation of the illegal drugs market.

We should stress the limits of the analysis conducted. Owing to constraints in terms of deadlines and contributors, it proved impossible to secure the specialist help of media sociologists. The articles were selected by different methods in the different countries, which may have led to some bias. We were also unable to conduct dual coding of the arguments investigated. The observations set out in this document must therefore be seen as the fruit of an exploratory investigation rather than a fully-fledged analytical study of content.

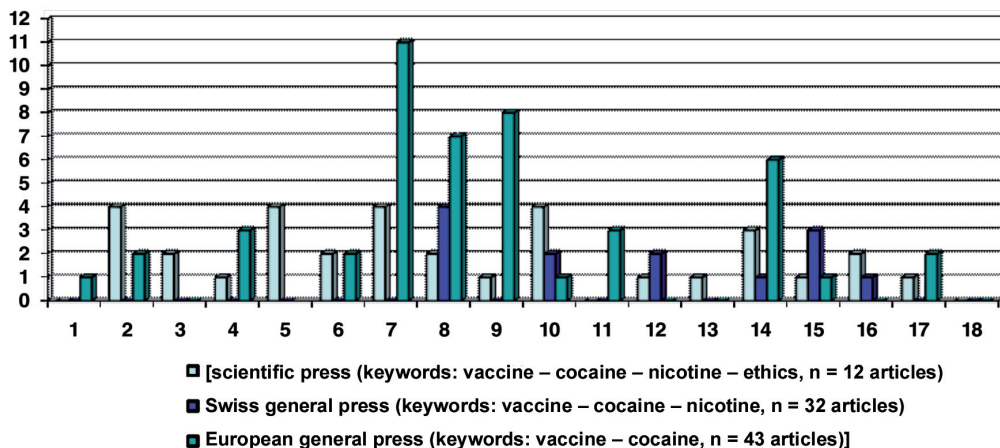
These limits notwithstanding, we consider that the analysis conducted confirms a highly systematic use of the word "vaccine" in public and political communication by the researchers. Should one use the word immunotherapy rather than vaccination? Does the lack of caution in the use of the infectious metaphor for addictive behaviours risk intensifying public lack of understanding of the specificity and complexity of the public health issues surrounding drug abuse? The deontology of the researchers and the biomedical contributors contains provisions to manage relations with the media. The aim is to provide reliable public information and not raise unfounded or disproportionate hopes of healing.



Appendixes: summary tables

Table 1: List of critical arguments identified in all the sources consulted

Arguments linked to the principle of autonomy	Arguments linked to the principle of beneficence	Arguments linked to the principle of non-maleficence	Arguments linked to the principle of justice	A piecemeal, reductionist approach
1. Difference between standard vaccines and the cocaine vaccine from the viewpoint of the patient's active involvement (drugs are actively sought out but not diseases).	6. Assessment of the suitability of vaccination in view of the person's characteristics, group of experts	9. Side-effects of vaccines	13. Is the aim to improve the well-being of individuals or society? Cf. standard vaccines: public health reasons whereas drugs do not cause epidemics.	14. Vaccination targeting a single substance.
2. The concept of consumer choice and self-determination	7. Use for the purposes of primary prevention.	10. Intentional overdosing to preserve the effects of the drug.		15. The term vaccine is not appropriate (according to the generally accepted definition it refers to infectious diseases).
3. Consent to vaccination and capacity for understanding.	8. Vaccination: a limited, one-off procedure	11. Modification of a neurobiological process, but are other changes brought about?		16. The right to full and accurate information: a public, political and media issue.
4. Compulsory treatment.		12. Indirect encouragement to take drugs through the perception that this is a simple remedy for addiction.		17. Exploitation of vaccination for ideological purposes, particularly the promotion of an ideology focusing on the goal of a "drug-free society".
5. Confidentiality				18. Failure to take account of the illegal drug market's capacity to adapt.



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INFORMED AND CONSCIOUS CONSENT IN MEDICAL RESEARCH INVOLVING DRUG DEPENDENT PERSONS AND DRUG USERS -

ETHICAL CHALLENGES

by Krzysztof Wilamowski, Lawyer, Poland, June 2010

Informed, conscious and free consent is the main guarantee of a patient's rights and safeguards from arbitrary and possibly harmful treatment when undergoing any medical activity. This issue has been discussed on so many occasions and described in so many scientific publications, that one has the impression, that everything is clear and the frames and rules are well known and undisputed. In fact, the issue of consent is so "well known", that often practitioners forget about the basis. The last statement is especially relevant in regards to medical research. As the number of industrially sponsored research is growing quickly, it is important to focus on a few ethical aspects of informed, free and – mainly – conscious consent. It is important for all patients and subjects who undergo medical research, but special attention has to be drawn to persons who are in a worse position from the beginning of their contact with medical staff, such as people dependant on various substances whose level of consciousness and ability to make a free choice is in many situations, highly limited.

On the other hand, constructing safeguards to protect from arbitrary intervention has to be done extremely carefully with respect to the right for privacy of the protected person. This is very important, particularly when assessing the motivation of a medical research volunteer.

The issues presented below shall be the subject of discussion. This paper is rather a general overview, with special focus on legal aspects and premises of informed and conscious consent rather than an exhaustive analysis of the topic. It is the tip of the iceberg, when thinking of possible ethical challenges in medical research involving drug dependant people.

1. Informed, free and conscious consent – basic aspects.

An informed, free and conscious consent should be guaranteed at a theoretical and practical level and comprise detailed safeguards, which should be fulfilled together for completion of the rule in question. These are:

- voluntary participation (in medical treatment, research etc.);
- complex information about the trial or research with free questions of volunteer and clarifications from personnel („knowledge exchange”), before the process begins;
- preferably written form of declaration to participate;
- freedom of withdrawal at any time;
- volunteer must be competent to give consent both legally and in fact.

First four of the above safeguards are undisputed and have a stable character. They also do not need to be widely described here. The fifth is more flexible as it lets, in some situations, the research to proceed when another person (parents, legal guardians) have consented on a volunteer's behalf (this person has to be legally capable and legitimate in order to give consent on behalf of the volunteer). It has to be stressed that, as a principle, the fifth safeguard excludes the consent given by mentally ill or retarded persons, as well as intoxicated people,

if they don't have legal guardians, which means in fact, if they are not incapacitated. However in practice, the consent of a drug dependant person can be treated as legally valid after stabilisation of a patient (stabilisation should consist of two stages: detoxification and the time for initial patient soothing). The consent given in such circumstances can be legally valid. but is it be sufficient on ethical grounds?

To answer this question we have to keep in mind a few matters described below on this point and in the next one, dedicated to the motivation of volunteers.

First of all, we have to remember about the head rule of the research (not only medical). It can be shown in following words:

In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject¹.

It means, that in any case, the ultimate value for the researcher or physician has to be the health of a volunteer (subject) in the scope of potential risk. The question is, if there are ethical (but not legal) doubts if the consent is fully conscious but, on the other hand, the risk of harm is no higher than the expected benefit (both assessed in the scope of the recent level of knowledge), can the consent given and the decision to include the volunteer into the research be acceptable on ethical grounds?

According to European standard, presented in Article 14 par. 3 of Additional Protocol to The Convention on Human Rights and Biomedicine, Concerning Biomedical Research, Where the capacity of the person to give informed consent is in doubt, arrangements shall be in place to verify whether or not the person has such capacity. Of course, in practice the assessment of this decision making process can be very difficult to undertake. However on a guidelines level, it seems to be the only reasonable solution. Besides, such interpretation is coherent with the attitude presented by Hebert²: "the patient's signature on a consent form following a rehearsal of facts by the physician may be considered legal consent. However, for true ethical consent to take place, the physician must feel that the patient understands his situation in its entirety, and that the decision the patient makes is based on this understanding is actually the best decision for that patient".

The situation of volunteers not able to express their consent (without capacity to consent) will be described in section 4.

2. Volunteer's motivation.

When assessing the consciousness of a consent given to participate in medical research, particular attention has to be drawn to the motivation of a volunteer. Assessment of various motivations can be crucial to understand the situation of persons dependant on substances,

1 Point 4 in Chapter III (Non-Therapeutic Biomedical Research Involving Human Subjects (Non-Clinical Biomedical Research) of Declaration of Helsinki, adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, and the 35th World Medical Assembly, Venice, Italy, October 1983; cite as British Medical Journal (7 December) 1996;313(7070):1448-1449; source: <http://www.cirp.org/library/ethics/helsinki/>

2 Hebert, P.C. (1996). Doing Right: A Practical Guide to Ethics for Medical Trainees and Physicians New York: Oxford University Press

such as psychoactive ones. It would be hoped by global society, and especially the researchers that medical research volunteers would want to help science and future generations. Such high motives for participation in research would appease the general conscience. However it is generally known, that this hope does not have any basis in practice.

We can find various sources confirming the statement expressed recently. For instance, J. McHugh³ showed few examples that every year, millions of volunteers participate in clinical trials in return for quick cash. What is most important, in many cases their participation is built upon simple and – undoubtedly at first glance – rational philosophy. One of the respondents, who participated in 60 medical trials during 10 years and earned from 30.000 to 60.000 USD, expressed why he participated in medical trials (being a medical rat simply) in following way: *“I’ve worked in construction and hit my thumb with a framing hammer. I’ve worked as an electrician and seen guys get electrocuted. Being a lab rat is the only work situation where you’ve got around-the-clock medical attention. It’s the safest job I’ve ever been in.”*

Is the “quick cash” motivation acceptable on ethical grounds? Even if the answer is negative, it has to be noticed, that there can be a conflict between morality (of society – in the general sense) and the right to a private life of an individual combined with her/his personal freedom⁴. Freedom of to seek an occupation and so called “style of life”⁵, which shall be interpreted as an integrated part of private life, are one of the fundamentals of human rights in a democratic society. Therefore even if the general ethics cannot accept such motives for participation in medical (or any other) research, it is not legitimated to forbid such practice. The reason for such an attitude is very simple: as to the principle, the motivation does not determine the consciousness of a person – even if the activity is against the public morals or ethical standards accepted in a particular group or society, it does not automatically means it is undertaken unconsciously.

If we agree that motivation for consent is separate from consciousness of the risks and potential outcomes of participation in medical research and that the motivation does not necessarily influence the level of consciousness, then the above conclusion can be appropriately applied to the participation of drug dependant persons in medical research. There are only two conditions that have to be fulfilled:

- the volunteer should pass the stabilization phase of the therapy;
- at the same time, while she/he is still in the therapy, the research should not influence the therapy in a negative way – the possibility of help is obviously higher than the risk of harm.

3 McHugh, J. (04/24/2007). Drug Test Cowboys: The Secret World of Pharmaceutical Trial Subject. Wired Magazine

4 Right to private life is guaranteed in Article 8 of ECHR. In this context, right to privacy means, among others, right to direct one’s life in a chosen way without any obstacles, with the exception of those stated in Article 8 par. 2 ECHR. Consequently, it partly “enters” the scope of personal freedom (Article. 5 ECHR), which can be explained as: the right to do anything, which is not forbidden.

5 The exceptions (limitations) of this freedom can be imposed only by Statute, which is the international (including Convention on Human Rights and Fundamental Freedoms) standard.

On the other hand, the above conclusion cannot be so simply applied to a person (volunteer) who suffers from active dependency from drugs, especially opiates. It is obvious, that in such situations, the level of consciousness is highly limited and motivation often concentrates on achieving the drug or sources to buy it. From both a legal and an ethical point of view each case has to be examined with extreme caution. The general rule – that the benefit is no smaller than the risk of harm – has to be assessed within the recent indications of medical knowledge as well as with regard to every individual's health condition. There should also be a predicted outcome of the research which is important for treatment of drug dependency. If it is not against the nature and the aim of the research, the volunteers actively using drugs should be stabilized⁶ before the trial begins. Obviously the last remark does not concern the volunteers who are non-users, forming, for instance, the control group.

As a conclusion to the above, in the author's opinion, the motivation has to be treated rather as an internal factor of each volunteer, rather than an element of assessment if consent is given consciously. The same applies to people who are dependant from drugs after stabilization phase.

3. Ethical challenges in research – example of research sponsored or conducted by industry.

The impact of industry sponsored research on the issue of free and conscious consent is still terra incognita. The reason for such a situation is the lack of credible data flowing from the evaluative trials which assess standards of medical research funded by industry. Currently we can only speculate on the basis of research not directly concentrated on free consent, but investigating the nature of research sponsored by industry and comparing it to those funded with other, "traditional" sources.

In this place we can point out a few matters which are important from the free consent point of view and which were shown, among others, by Australian⁷ research. These are:

- delayed publication of results;
- non-publication of results;
- concealment of results;
- first drafts of the reports written by the industry staff.

Those examples of research malpractice can impact on the issue of free and conscious consent, by the violation of quasi-agreement which is concluded by a volunteer and a researcher before the trial begins. It is the author's assumption that many of volunteers (regardless of their basic motivation) give their consent to participate in research hoping its results will be published

6 The stabilization process should consist of physical and/or mental stabilization. It should result in the possibility for a volunteer to be fully capable to understand the reasons and risks of the research in question. The separate issue is the body (or person) which would be legitimated to assess the effect of the stabilization. It seems reasonable that such a decision should be undertaken by someone not directly involved in the research (to avoid vagueness and accusations of lack of objectivism).

7 Henry D. A., Kerridge I. H., Hill S. R., McNeill P. M., Doran E., Newby D. A., Henderson K. M., Maguire J., Stokes B. J., Macdonald G. J., Day R. O. Medical specialists and pharmaceutical industry-sponsored research: a survey of the Australian experience. MJA 2005; 182 (11): 557-560

and – preferably – helpful. Of course, it is the matter of motivation, described in point 2, which we can assume, that a certain percent of volunteers do not give their consent to participate, if they know, the publication can be cancelled, delayed significantly or the results which are not in favor of a sponsor's products will be concealed in this or another way.

The practice of concealment of results containing negative key findings and on the other hand, publicizing results favoring the sponsor's product in industry sponsored research was confirmed also in other research on this topic⁸. However it is hard to assess the scale of this phenomenon without more specific and wider research.

Ethical challenges are obvious in the field of medical research sponsored by industry as well as other external (to the medical personnel) sources. However it is very hard to find solutions, which can be introduced in practice. For example, the states could implement into their national legislation an obligation to register (to notify) an undertaking of the research in any case (including private and industry sponsored research). It should be a simple notification, without obligation to obtain a permission by an authority. Later, after completion of the research the performer should have an obligation to inform the proper authority about the results of a research. The results sent to the authority could be accessed by the public. However, this solution ensures only the publication of the results and information on undertaking the research. At the same time, there is no guarantee, that the results provided by the performer will truly show actual results obtained. Besides it has to be expected, that industry will defend themselves from the obligation to notify research implementation by raising the issue of commercial (trade) secrecy.

Of course, there are some European standards which require the publication of research results. Article 28 of Additional Protocol to The Convention on Human Rights and Biomedicine, Concerning Biomedical Research states that:

1. On completion of the research, a report or summary shall be submitted to the ethics committee or the competent body.
2. The conclusions of the research shall be made available to participants in reasonable time, on request.
3. The researcher shall take appropriate measures to make public the results of research in reasonable time.

In principle the above directives determine the proper direction, lack of sanctions or precise regulations in the matter of publication of the results, is enigmatic. The issues such as appropriate measures or reasonable time can be easily used in practice to avoid responsibility for concealment of results or delaying its publication. However, the respective bodies implementing the Protocol's provisions can and should use functional interpretation of this enactment, to make it fully effective.

Either way, the issue of sponsored medical research raises a lot of ethical issues. Even if now it is not possible to find and work out certain guidelines, ethics should carefully observe the development of this part of medical research.

8 Lexchin J., Bero L. A., Djulbegovic B., Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003;326:1167-1170 (31 May)

4. Research on drugs and the case of drug users as volunteers.

The matter of informed and – especially – conscious consent with regard to research on drug addiction and participation of drug users as such is quite complicated. In the light of the aforementioned remarks, it is often very difficult to assess if a drug dependant person is capable or incapable (depending on their actual mental condition) to consent to take part in research of such kind. On legal grounds, doubts can be eliminated by provisions of above mentioned Additional Protocol to The Convention on Human Rights and Biomedicine, Concerning Biomedical Research. In the scope of Article 14 par. 3 of the Protocol it would be very helpful to work out the standard of arrangements that should be made to verify whether or not the person has the capacity to give informed consent. There is then the question, what if the results of those arrangements will show, the person has not such an ability. According to European standard, such persons are not generally excluded from participation in medical research. However a number of conditions have to be fulfilled, to protect their rights. As the addition to Article 14 par. 3 (cited above) of Additional Protocol it is worth quoting here Article 15:

Article 15 – Protection of persons not able to consent to research

- 1** Research on a person without the capacity to consent to research may be undertaken only if all the following specific conditions are met:
 - the results of the research have the potential to produce real and direct benefit to his or her health;
 - research of comparable effectiveness cannot be carried out on individuals capable of giving consent;
 - the person undergoing research has been informed of his or her rights and the safeguards prescribed by law for his or her protection, unless this person is not in a state to receive the information;
 - the necessary authorisation has been given specifically and in writing by the legal representative or an authority, person or body provided for by law, and after having received the information required by Article 16, taking into account the person's previously expressed wishes or part in the authorisation procedure. The opinion of a minor shall be taken into consideration as an increasingly determining factor in proportion to age and degree of maturity;
 - the person concerned does not object.

- 2** Exceptionally and under the protective conditions prescribed by law, where the research has not the potential to produce results of direct benefit to the health of the person concerned, such research may be authorised subject to the conditions laid down in paragraph 1, sub-paragraphs ii, iii, iv, and v above, and to the following additional conditions:
 - the research has the aim of contributing, through significant improvement in the scientific understanding of the individual's condition, disease or disorder, to the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons in the same age category or afflicted with the same disease or disorder or having the same condition;
 - the research entails only minimal risk and minimal burden for the individual concerned; and any consideration of additional potential

benefits of the research shall not be used to justify an increased level of risk or burden.

- 3** Objection to participation, refusal to give authorisation or the withdrawal of authorisation to participate in research shall not lead to any form of discrimination against the person concerned, in particular regarding the right to medical care.

It is obvious, in the author's opinion, that this provision can be directly applied to medical research on drug addiction, where the volunteers are people suffering from an active form of dependency from drugs. Therefore we can distinguish two situations:

- the results of the research have the potential to produce real and direct benefit to a volunteer's health (paragraph 1);
- the research has not the potential to produce results of direct benefit to the health of the person concerned (paragraph 2).

It seems that, in practice – with regard to drug users and drug dependant persons – a more common situation will be where the results of the research will not have the potential to produce direct benefit to the health of the volunteer. However it is undisputed that the research on drug addiction should aim to contribute, through significant improvement in the scientific understanding of the individual's condition, disease or disorder, to the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons in the same age category or afflicted with the same disease or disorder or having the same condition (Article 15 par. 2 sub-par. i). In other words, the research should aim to produce indirect benefit to the health of the population (or part of it) of drug users. Thus it seems that after following other conditions stated in the discussed provisions, the participation of drug users and drug dependant persons can also be acceptable on ethical grounds. It is not an obstacle that such research can be undertaken exceptionally – the drugs phenomenon has to be treated as an unusual case or even an “emergency state”.

Few words should be devoted to the matter of the necessary authorization, pointed out in Article 15 par. 1 sub-par. iv. It might suggest, that the regulation is only in respect of legally incapacitated persons. But when we look at the beginning of Article 15, we find a statement relating to a person without the capacity to consent. There is no basis for restrictive interpretation of this provision and narrowing the term used only to incapacitation in the legal sense. It has to be then interpreted extensively, including also lack of capacity (physical or mental) at the time of consenting. Accordingly, the necessary authorization, will be required not only in cases regarding legal incapacitation and minors, but also – as it seems – in cases of persons without the capacity at the time of consenting. In the second situation, the authorization, can be initiated, for instance, by lodging a motion to a court for establishing a guardian for a person in question. The rest of the authorization process will proceed after the court's ruling.

Above remarks do not cover participation of other people (who were not and are not using illicit drugs, so in consequence they cannot be drug dependant) in research on drug addiction. Once again we can distinguish two situations:

- participation of volunteers able to consent consciously to take part in a research;
- participation of volunteers not able to consent consciously to take part in a research.

The first group will be the subject to general rules and guarantees of informed and conscious consent, which were described in above parts of this report. The only remark which has to be made here: as a principle, members of this group are generally entitled to give consent to take part in researches in question. The matter of ethical reservations regarding undertaking researches where an illicit drug is administrated to non-user, exceeds the frameworks of present analysis.

With regard to the second group, it has to be stressed that it is very hard to imagine, that the effectiveness of the research can be reached only if the volunteers consist of incapacitated persons not using drugs. Thus, if research of comparable effectiveness can be carried out on individuals capable of giving consent (Article 15 par. 1 sub-par. ii), there is neither legal nor ethical reasons to accept such situation. Then the answer to this question is if an ethics committee could accept the administration of an illicit substance to a naïve subject must be negative.

5. Conclusions.

Lack of research on the issue of free, informed and conscious consent makes it hard to point out more potential problems in practice. The points shown above seems to be a ground for discussion, if in fact the issue in question is fully safeguarded from any violations.

Next years, together with the development of medical research sponsored by industry and other external sources should also bring a response to the question if the volunteers in these research are not treated as “subjects” in the most pejorative sense, as they are only used to “prove” the initial assumption that the best product comes from the sponsor of a particular research.

An issue of participation of drug users and drug dependant persons in medical research as well as the research on drug addiction is undoubtedly complicated. Bearing in mind the provisions of Additional Protocol to The Convention on Human Rights and Biomedicine, Concerning Biomedical Research the effort should be made within the countries, which are potential parties to this agreement, so it will come into force as soon as possible⁹. The reason is not only the matter of above described provisions on consent to the research, but especially the role of ethics committees in the process of approval and evaluation of each research project (Articles 8-11).

9 The current status of signatures and ratifications is not optimistic. Countries such as France, Sweden, United Kingdom, Ireland, Poland did not even sign the Protocol. Current status of signatures and ratifications can be found at Council of Europe website: <http://conventions.coe.int/Treaty/Commun/ListeTableauCourt.asp?MA=9&CM=16&CL=ENG>

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