Vaccine 37 (2019) 5485–5490

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

The continuing search for an addiction vaccine

M. Heval Ozgen [a,*], Stuart Blume [b]

[a] Parnassia Psychiatric Institute and Addiction Research Center (PARC), Interculturel Psychiatry (i-psy), Parnassia Academy, The Hague, the Netherlands
[b] Department of Anthropology, University of Amsterdam, Amsterdam, the Netherlands

ARTICLE INFO

Article history:
Received 29 September 2018
Received in revised form 27 April 2019
Accepted 24 June 2019
Available online 29 June 2019

Keywords:
Addiction
Synthetic opioids
Metabolites
Unconventional carriers
Behavioural endpoints
Ethics

ABSTRACT

Inspired by advances in immunology, in the 1970s scientists began to study the possibilities of mobilizing the human immune system against intruders other than pathogenic viruses and bacteria. In 1972 the suggestion was first made that it might be possible to provoke immunity to narcotic dependence. Because molecules of narcotics such as heroin and cocaine are too small to stimulate an immune response, researchers sought ways of coupling them to immunogenic proteins. The substances they developed soon became known as addiction vaccines. However, despite fifty years of research, and despite the growing problem of addiction, no vaccine against heroin, cocaine, methamphetamine or nicotine addiction has yet been licensed for clinical use. This paper reviews the history of addiction vaccinology, seeks to explain the unique appeal of a vaccinological approach to addiction, and argues for broad discussion of how such vaccines should ultimately be used.

1. Introduction

From hesitant beginnings more than a century ago, vaccination against infectious diseases has become a keystone of today's global health. Its prime objective is of course to save lives. Vaccines have saved countless lives, and despite 19th century resistance to compulsory smallpox vaccination, and despite today's 'vaccine hesitancy' [1], most people accept that this is what it does. Moreover, when experts warn of an impending epidemic, hopes are immediately pinned on a rapidly-to-be-developed vaccine against Ebola for example, or Zika. The spate of dystopian films and TV series indicate how this faith in vaccination as the principal source of hope, of salvation, has become embedded in popular culture [2]. This may be particularly true of the United States, with its distinctive faith in the possibility of technological solutions to problems of health and society [3,4].

The existence of a new vaccine does not in itself determine how it will be used. Both with rubella and more recently with HPV the objective of vaccination was changed from protecting individual girls to halting circulation of the virus. When a vaccine against hepatitis B became available some countries limited vaccination to defined risk groups, because the disease was rare and the vaccine expensive. However, faced with a recommendation from the WHO, and with the argument that demarcating risk-groups was problematic, the policy was largely abandoned.

Understanding of how precisely vaccines work grew more slowly than their use in practice. However developments in the field of immunology led to the realization that it should be possible to mobilize the immune system in tackling intruders other than infectious pathogens. Researchers then began to study the possibilities of creating vaccines against a variety of very different conditions. These include breast cancer [5], conception [6], Alzheimer's disease [7], obesity [8], and addiction.

Building on developments both in immunology and in neurochemistry, in the 1970s scientists began to study ways in which molecules of addictive substances such as cocaine, heroin and methamphetamines, as well as nicotine could be modified so as to elicit an immune response. The substances that they synthesized soon became known as addiction vaccines. In this paper we first review the history of attempts at developing addiction vaccines, and the challenges they face. Few candidate vaccines have entered Phase III trials. Though none has as yet proven successful researchers are undeterred. This study aims to examine what lies behind the continuing appeal of an addiction vaccine, and suggest that consideration should be given to the ways in which these vaccines might eventually be used.

2. History of addiction vaccinology

At the start of the 1970s illegal drug use in the United States was rising. There were fears that returning Vietnam veterans

* Corresponding author at: Parnassia Addiction Research Centre, Parnassia Academy, Kiwistraat 43, 2552 DH Den Haag, the Netherlands.
E-mail address: m.h.ozgen@parnassiagroep.nl (M.H. Ozgen).

https://doi.org/10.1016/j.vaccine.2019.06.074
0264-410X/

would add to the ranks of the 'junkies' already present in the inner cities [9]. In 1971, President Nixon declared drug abuse 'America's public enemy number one', and 'the war on drugs' was launched. For years the emphasis had been on penalizing drug-related criminal behaviour, and the 1956 Narcotics Control Act had introduced measures that could extend to life imprisonment or even the death penalty [10]. While the US Department of Justice continued to prioritize the criminal behaviour associated with illegal drug use, support for the idea of addiction as a brain disease was gaining ground [11]. This support rested on a growing body of neuroscientific research, notably Snyder and Pert's 1973 discovery of opiate receptors. In 1974 a National Institute on Drug Abuse (NIDA) was established in the National Institutes of Health, additional funding for research became available, and the first explorations of the possibility of vaccinating against drug dependence took place.

Work began in the late 1960s, when Spector and Parker converted morphine to carboxymethylmorphine and dissolved it in distilled water containing a protein, bovine serum albumin (BSA) in the presence of carbodiimide, a reactive agent that links small molecules to carrier proteins. Having then injected rabbits with an emulsified version of this mixture, they showed that the rabbits' blood contained antibodies bound to the morphine molecule [12]. The authors stated that this was the first description of experimental production of morphine-specific antibodies. Whether these morphine antibodies would interfere with the pharmacological effects of morphine was still to be investigated. In 1972, Berkowitz and Spector published first results of their studies of the response of mice to morphine, concluding that the body's growing tolerance of narcotics could involve an immune-like mechanism [13]. Berkowitz and Spector had established the principle of anti-addiction vaccination, and were convinced that immunity to narcotic dependency was at least conceivable. Immunologically, molecules of cocaine and heroin are haptens; they are too small to stimulate an immune response themselves, but they can be covalently coupled to an immunogenic protein by means of conjugation, using an agent such as carbodiimide. The hapten-protein conjugate can be made to elicit antibodies against the hapten, which will then recognize and respond to the drug molecule. Moreover, and crucially, the compound molecule will be too large to cross the blood-brain barrier. Held in the bloodstream, entering the brain either not at all or at least much more slowly, little or no euphoric effect will be experienced. In 1974 researchers from the University of Chicago described experiments on a rhesus monkey trained to self-administer heroin and cocaine [14]. They subsequently showed that an emulsion containing a morphine compound bound to BSA facilitated the clearance of morphine from the bloodstreams of eight rabbits [15]. Few researchers picked up on these findings at the time, and with rising expectations of maintenance programs based on using the synthetic opioid methadone, this work came to a halt.

3. New beginnings

In the 1990s attempts to develop anti-addiction vaccines resumed. Not only was the scale of the problem continuing to grow, but it seemed that existing approaches were failing. The high relapse rate among drug users seeking treatment made it imperative to develop new treatment options for this disease [16]. Researchers found that only a quarter of heroin addicts remained abstinent after completing the methadone maintenance treatment. After three months the majority had relapsed, continuing to use illicit drugs and in many cases to commit crimes [17]. Though the first studies had focused on morphine and heroin, in the 1990s the focus was principally on nicotine, cocaine, and methamphetamine. Unlike heroin and morphine, there are no approved pharmacological options for treating cocaine or methamphetamine addictions, and development of one was a NIDA priority.

3.1. Nicotine

The motivation to develop a vaccine against nicotine addiction reflected concern at the high smoking-related morbidity and mortality, especially among younger age-groups [18]. In the case of nicotine abused doses are much lower than with heroin or cocaine, so that smaller quantities of antibody should be sufficient to attenuate its effects. Nicotine therefore seemed a particularly good candidate for this approach [19]. First generation vaccines against nicotine addiction included one, NicVax (developed by Nabi Pharmaceuticals/GSK), which reached Phase III clinical trials. The vaccine consisted of a nicotine derivative (3′-amino-methyl-nicotine) conjugated to a protein (detoxified Pseudomonas exoprotein A). The vaccine gave promising results in a randomized multicentre phase II controlled trial among 301 smokers. However in two-phase III trials vaccine recipients were no more likely to cease smoking than those given a placebo. Neuroimaging studies carried out thereafter gave inconclusive results [20]. Three other first generation protein conjugate vaccines (NiQb/Nic002, TA-NIC, and Niccine) were tested in Phase II trials. In all cases the antibody response generated was too weak and the response of individuals proved to be highly variable. By 2014 an editorial in the journal *Addiction* questioned the need for large-scale investment in nicotine vaccine development, given the range of other treatment options [21]. The search for a nicotine vaccine has continued nevertheless. Second generation vaccines include synthetic nicotine-like haptens conjugated with diphtheria toxin, as well as others using different carrier proteins and different adjuvants. Most studies have been conducted in mice, though one phase I trial has taken place [20]. Currently a number of novel approaches to vaccine design, believed to have certain advantages over first generation vaccines, are being tested in laboratory studies. These include nanoparticle-based vaccines, in which a nanoparticle surface replaces the conventional protein, and others conjugating nicotine to a liposome complex. One or two of these novel vaccines have reached the stage of Phase I trials [22,23] though most are still at the laboratory stage. A useful review of the current state of nicotine vaccine development is given in [20].

The social and political pressures to produce vaccines against cocaine and heroin addictions are more complex. In addition to rapidly rising drug-related morbidity and mortality, and the lack of any approved cocaine pharmacotherapy, they also derive from longstanding politico- legal interests in controlling narcotics trade-related criminal behaviour.

3.2. Cocaine

In the mid to late 1990s a number of candidate cocaine vaccines were tested on rodents. In 1995 researchers at the Scripps Research Institute in La Jolla described the synthesis of a vaccine they named GNC-KLH. Produced by conjugating the hapten to a protein (keyhole limpet hemocyanin, or KLH), and adding an adjuvant known as MPL-TDM, this reduced levels of cocaine in the brain tissue of immunized rats by 80% compared to controls [24]. In 1997, Fox et al studied a vaccine made by conjugating succinyl norcocaine to BSA. They were able to show that this vaccine elicited high titre antibodies in mice. Fox cautiously concluded that a therapeutic vaccine could be an effective tool in the treatment of recovering cocaine addicts. And although "the vaccine will not be a 'magic bullet'", the researchers were convinced that it would be useful in reducing the recidivism rate among cocaine addicts. They warned, however, that addiction is a complex phenomenon, and

that a mix of pharmacological and psycho-social strategies would always be needed [25].

Kosten's group, then at Yale, began human studies of a vaccine made from succinyl norcocaine conjugated to a cholera toxin, with an aluminium hydroxide adjuvant, and later named TA-CD. In the first Phase II trial 18 subjects were given either a high or a low dose vaccine. Despite initially high antibody titres these fell rapidly in both groups, and after six months there was a high relapse rate [26]. A phase III trial, involving 300 participants at six centres across the USA, examined the effects of five doses of TA-CD administered over a period of eight weeks. Subjects provided urine samples, self- reported cocaine use, and were offered cognitive behavioural therapy (CBT). Despite initially promising results, the conclusions from the trial were mixed. Even when adequate antibody levels were attained, these did not correspond to significant reduction in cocaine use [27]. Looking at different sub-groups, these authors conclude that the vaccine may have therapeutic value for some cocaine-dependent patients. However, those who were insufficiently motivated would be able to override the partial blockade provided by the vaccine [27]. An additional problem was the difficulties investigators faced in recruiting participants to the study. They explain that it took seventeen months for them to recruit 300 sufficiently motivated addicted persons from the multiple study sites. This suggests, they conclude, that even an effective vaccine may be no more attractive to the cocaine-abusing treatment population than current psychosocial strategies.

In 2013 a different experimental cocaine vaccine was announced. Termed dAd5GNE, it was made from a cocaine hapten named GNE conjugated to a surface protein of a disrupted adenovirus. Preliminary studies of the effects of dAd5GNE on mice and rats showed that it prevented cocaine-induced hyperactivity. A later study in rhesus monkeys led to the conclusion that the vaccine may have therapeutic potential, as part of a relapse-prevention strategy, with human patients who achieve cocaine abstinence [28]. In 2016, with funding from NIDA and the NIH, the dAd5GNE vaccine advanced to clinical trials. The trial would enrol three consecutive cohorts, each made up of ten active cocaine users. Each participant would have to commit to giving up cocaine for at least thirty days and having their urine tested for cocaine use during this period. After an initial dose, given as an injection in the shoulder, booster shots would be given every four weeks, until six in total had been given by week twenty. Thereafter subjects would be monitored for a further three months. The study would end after thirty-two weeks [29]. Second generation cocaine vaccines, looking to improve immunogenicity, make use of conjugation to nanofibers, or to flagellin, a bacterial protein that itself produces an immune response, or make use of combination strategies involving the co-administration of the vaccine with cocaine degrading enzymes or gene therapy.

3.3. Methamphetamines (MA)

In the late 1990s researchers at the Korea Institute of Science and Technology attached three different forms of amphetamine to two different proteins, added an adjuvant, injected the mixtures into goats, and so obtained antisera from the goats. The objective of the work was to develop an accurate means of assessing the quantity of (meth)amphetamine in urine [30]. As with cocaine, no approved pharmacotherapies are available for treating MA disorders. Because methamphetamines are cleared far more slowly than cocaine the route toward a vaccine here has been via production of monoclonal antibodies used for short-term rapid action. Owens and his colleagues at the University of Arkansas for Medical Sciences have produced methamphetamine monoclonal antibodies, which can be used in treating overdose [31].

Attempts to develop active conjugated vaccines are continuing in a number of laboratories, though none have moved beyond the pre-clinical stage. One candidate vaccine consists of succinyl methamphetamine conjugated to tetanus toxoid, adsorbed on aluminium hydroxide. Kosten's group have been studying this vaccine in the presence of various adjuvants, including a novel phospholipid adjuvant called E6020. This has been shown to generate promising levels of antibodies in mice [32].

3.4. Opioids

For a number of reasons, opioids pose particular problems to vaccine developers. One is the fact that many of them are needed and widely used as prescription painkillers. Another is the fact that they typically metabolize in the body, producing additional psychoactive substances. For example, when heroin metabolizes it yields three distinct psychoactive metabolites, including morphine. Thus whilst morphine and heroin were the earliest focus for development of an addiction vaccine, it was initially unclear whether an effective vaccine would have to elicit antibodies against heroin as well as all its active metabolites. A preparation that works against one derivative would not necessarily work against all. A decade ago, Anton and Leff at the National Institute of Psychiatry in Mexico City were able to conjugate a morphine derivative to a tetanus toxoid surface protein, and to show that this produced antibodies against both heroin and morphine in rats [33]. But the antibodies did not persist for long and vaccinations had to be repeated at very short intervals, limiting its use in practice. In 2011, the Scripps research group published results of studies of different heroin vaccines tested on rats. Two of their vaccines seemed to be successful both in producing antibodies and influencing addicted rats' tendency to self-administer heroin [34]. Optimism seemed justified, and the researchers envisaged their vaccine facilitating clinical management. Provided the results seen in rats could be replicated in humans, the vaccine could provide a useful option to be used in tandem with opiate replacement therapy [34]. Janda and his colleagues continue to investigate different heroin vaccines, using different haptens, different proteins, and different adjuvants. A vaccine conjugated on tetanus toxoid, with both alum and CpG oligodeoxynucleotide adjuvants, has recently appeared promising in both mice and rhesus monkeys, with effects lasting for eight months [35].

Abuse of synthetic opioids, such as oxycodone and fentanyl, widely used as painkillers is a major factor in the current scale of overdose-related deaths [36]. Scientists in a number of centres including the Scripps Research Institute [37] and the Minneapolis Medical Research Foundation [38] are exploring the feasibility of developing vaccines that would combat overdose and addiction to these.

4. Taking stock

The search for an addiction vaccine, whether against nicotine, cocaine, heroin, or synthetic opioids, faces many challenges, some of which are biomedical. Despite many successes in animal studies, the only first generation vaccines to reach Phase III trials (NicVax and TA-CD) proved unsuccessful. A major problem in all earlier studies has been the weak antibody responses generated, despite the variety of haptens, carrier proteins, and adjuvants that have been used. The TA-CD study suggested, significantly, that even when high antibody levels were attained this did not necessarily translate to significant reduction in cocaine use. Translating between the endpoints of laboratory studies and endpoints involving a behavioural component is by no means straightforward. Some of the challenges the field faces are rather different. For

example, funding is a problem with most funding up till now having been provided by the NIDA. Addiction is seen as a marketer's nightmare, involving as it does a stigmatized condition and a "criminal" market. Partly for this reason there is little industrial interest in this work. Major pharmaceutical companies have been unwilling to support it [39,40].

Some of the challenges derive from the ease with which even a clinically effective vaccine might be circumvented. Thus, reflecting on the results of their TA-CD study, Kosten et al point to their difficulties in recruiting participants. They also note the facility with which insufficiently motivated addicts can override the effects of a vaccine by increasing their dose [27]. They might also turn to a different drug, or try to obtain the 'dopamine rush' they need in some other way.

Despite setbacks extending over four decades, despite critique such as this, scientists and the NIDA remain deeply committed to this work [41]. The search continues, with researchers now focusing on 'second generation vaccines', involving increasingly complex haptens and adjuvants, and conjugation to nanofibers in place of the hitherto conventional proteins.

5. The appeal of an addiction vaccine

The worldwide use of addictive drugs is an increasing medical, social, economic, and political problem. There are millions of users of illicit drugs worldwide, of whom relatively few have access to appropriate treatment. Despite decades of limited success, the hope persists that, by analogy with infectious disease epidemics, the 'opioid epidemic' can be controlled by vaccination. What makes the idea of an addiction vaccine so appealing?

The problem of addiction is large, serious, and costly. But what exactly is the problem? Is it deprivation, or a sense of hopelessness, that leads more and more people to turn to drugs, as many have suggested? Is it the criminal behaviour that they engage in in order to satisfy their craving, as law enforcement agencies see it? Or should it be equated with processes occurring in addicts' brains, as implied by the brain disease model of addiction? [11] Both theoretically and in practice the addiction field is highly contested [9,42]. The history of addiction policies displays an uneasy dynamic, with emphasis shifting between therapeutic and judicial-penal approaches, and with little consensus between them. Whatever combination of psychotherapy and pharmaceuticals is used, modes of treatment focused on the suffering individual will be difficult to scale up sufficiently, and are unlikely to satisfy those whose priority is control of drug-related crime. Much addiction-related public expenditure goes on law enforcement, and other measures unrelated to health care. Each perspective has its supporters among researchers, professionals, and policy makers; groups which, according to historian David Courtwright, continue to wrestle for control of the addiction field [11].

To be viable, a solution will have to be more or less acceptable to all major stakeholders, including those committed to therapeutic approaches and those committed to approaches relying on control and regulation. Not all conceivable strategies are likely to be able to count on this. Recent analyses of America's opioid epidemic attribute it, in great measure, to over-prescription of opioid painkillers [36,43]. The addiction of many people who eventually overdose on heroin or a synthetic opiate begins with a legally prescribed painkiller. In the United States the pharmaceutical industry is said to have lobbied effectively to block attempts at Federal regulation of opioid prescribing. Earlier lawsuits against tobacco companies have now inspired attempts to hold the manufacturers of opioid painkillers legally responsible for abuses [44]. However controlling the opioid epidemic by regulating physicians' prescribing of opioids for pain relief is a strategy which is unlikely to attract much support either in the medical profession or from the pharmaceutical industry. Yet, to be sustainable in the long term, any solution will have to be more or less acceptable to both.

Here we can see why the prospect of addiction vaccines is uniquely attractive. The appeal of an addiction vaccine goes beyond the expectation that, unlike maintenance drugs such as methadone, they would be long-acting. Vaccination has an ambiguous character. In the course of the past century vaccines have become central in controlling the spread of infectious disease, whilst parents have largely accepted vaccination as in the interests of their own child's health. For decades it has been widely accepted that preventative vaccination inhibits the spread of noxious agents through a community. To refer to the opioid-protein conjugates now under development as 'vaccines' is to vest them with a symbolic history: a history both of protection and of control. It is to evoke confidence that addiction can be 'fixed' technologically, like smallpox in the past, cervical cancer or polio in the present, or malaria or HIV in the future. Some commentators have suggested that instead of terming these substances 'vaccines' they should more properly be termed 'immunotherapies' [45,46]. Their argument, like Bydlowska's, is that terming them 'vaccines' leads to false expectations. Yet precisely here, in these ambiguous implications, lies the strategic value of referring to 'vaccines'.

Used appropriately, vaccines have been proven to facilitate control of challenges to a nation's wellbeing. From a political perspective drug addiction, like HIV, is just such a challenge. For a physician, faced with patients trying to control a craving, or overdosing, addiction is quite a different kind of challenge. Addiction vaccination has unique appeal precisely because it suggests a solution to each of these challenges.

6. How will the vaccines be used?

There is little discussion of how addiction vaccines would be used once licensed. Scientists developing them generally state, or imply, that, the vaccines will eventually be incorporated into existing therapeutic regimes. Perhaps in combination with existing drugs, their principal use would be in treating overdose and in preventing relapse among people undergoing treatment. Today's experimental vaccines could not be used otherwise since the antibodies they induce only persist in the body for a few weeks. In other words, they will be most effective in patients who are committed to their treatment [47]. In Olson and Janda's view treatment would make use both of vaccination and of opioid replacement therapy; i.e. with methadone. And since heroin is often laced with fentanyl on the street, there is a need to explore the feasibility of combination vaccines that would work against both. Avoiding any claim that these vaccines are magic bullets, Olson and Janda emphasize that when clinically available, vaccines will simply offer individuals suffering from OUD [opioid use disorder], who wish to control their addiction, another tool to help them do so [47].

It is by no means self-evident that this is how the vaccines would be used. Two decades ago the suggestion was made that they could, and perhaps should, be used preventatively rather than therapeutically. In 1997 a leading American addiction researcher recognized that once cocaine vaccine had been shown to be safe and to work, the question of 'who will be vaccinated' would become inescapable.

Should the vaccine be used in the absence of addiction or criminal conviction, but when an individual or population is deemed to be susceptible to addiction? Mandatory vaccination of targeted populations outside the criminal justice system is fraught with potential for prejudice, discrimination and unfairness. As a result, this approach would face severe constitutional challenge. Paradoxically, these problems would be obviated if society adopted the

obvious and inevitable policy of mandatory universal vaccination [48].

Since identifying at risk groups is likely to prove controversial, the problem could be avoided by vaccinating the whole population. Likening addiction to an infectious disease, a then-striking analogy which has since become commonplace, Cohen emphasizes the social nature of the infection involved. Even though the mechanism differs from that of an infectious disease epidemic, the fact that drugs are shared or sold is also a means by which an affliction is spread. So, he asks "why not institute universal mandatory immunization once a cocaine vaccine is available? There is ample legal support for the state's application of police power when necessary to act in the interests of public health" [48].

As research advances, and antibodies can be sustained in the body for longer and longer, these questions will gain in significance. Thus Olsen and Janda suggest that, in theory, opioid vaccines could be used prophylactically in at-risk populations [47]. Similarly Gartner Carter & Partridge argue that regarding addiction as a brain disease implies that individuals at risk of becoming addicted could be identified. Preventive measures, such as vaccination, could focus on these individuals. This might be preferable to a strategy aimed at an entire population [49].

Though there has been little discussion of the implications of these vaccines, the ethical problems lying in wait have been acknowledged. An expert group of the Council of Europe warned of the need to protect human rights, and to secure informed consent, were proposals to be made for the vaccination of offenders. This expert group warns of the ethical problems entailed by preventive vaccination even of consenting adults. There are still stronger objections to routine preventive vaccination of children or adolescents, comparable to routine immunisation against childhood diseases. Such practice, they argue, could not be justified [46]. Similar arguments have been put forward by Professor Wayne Hall, of the University of Queensland. He too has warned that use of the term 'vaccine' may lead parents to anticipate prevention of dependence in their children [50]. The right of parents to decide on this vaccination for their children is likely to be contested. Hall and Gartner also note that far more rigorous evidence would be needed for preventative rather than therapeutic use, and neither industry nor the community seems likely to underwrite such studies. Italian ethicists have recently put forwards similar arguments [51].

There is no doubt that any proposal for widespread or mandatory vaccination against an addiction would run into major ethical objections [52]. But ethical debates are unlikely to determine the outcome of political decision-making when addiction vaccines are eventually licensed. Although nothing came of it, more than a decade ago the British government was already said to be considering the preventative vaccination of children against future drug addiction. The history of vaccination against infectious diseases gives some insight into the temptations to which politicians will be subjected by the availability of addiction vaccines. Current disease eradication programs could easily inspire the conviction that through mass vaccination the problem of drug abuse and addiction could be solved once and for all.

7. Conclusions

It is far from clear when the first vaccines against opioids, nicotine, or any other addictive drug will be licensed for clinical use. Nevertheless discussion of how they would be used should not wait. The social, ethical, and political issues are complex. The clinical availability of these vaccines will add further to the complexities of treatment and of control that make the addiction field so controversial. Discussion has to take place before addiction vaccines are licensed and available. By that time, as competing interests come into play, it will be too late for measured evidence-based discussion.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors would like to thank Dr J. Hendriks for his comments on an earlier draft of this paper.

Declaration of Competing Interest

None.

References

[1] Schuster M, Eskola J, Duclos P. Review of vaccine hesitancy: rationale, remit and methods. Vaccine 2015;33:4158. https://doi.org/10.1016/j.vaccine.2015.04.035.
[2] Blume S. Immunization. How vaccines became controversial. London: Reaktion Books; 2008.
[3] Rothman DJ. Beginnings count. The technological imperative in American health care. New York and Oxford: Oxford University Press; 1997.
[4] Leshner AJ. We can conquer drug addiction. Futurist 1999;33(9):22–5.
[5] Emens LA. Breast cancer immunobiology driving immunotherapy: vaccines and immune checkpoint blockade. Expert Rev Anticancer Ther 2012;12 (12):1597–611. https://doi.org/10.1586/ERA.12.147.
[6] Naz RK. Recent progress toward development of vaccines against conception. Expert Rev Vaccines 2014;13(1):145–54. https://doi.org/10.1586/14760584.2014.869420.
[7] Bachmann MF, Jennings GT, Vogel M. A vaccine against Alzheimer's disease: anything left but faith? Expert Opin Biol Ther 2019;19(1):73–8. https://doi.org/10.1080/14712598.2019.1554646.
[8] Monteiro MP. Obesity vaccines. Human Vaccines Immunother 2014;10 (4):887–95. https://doi.org/10.4161/hv.27537.
[9] Satel S, Lilienfeld SO. Addiction and the brain disease fallacy. Front Psychiatry 2014;4:141. https://doi.org/10.3389/fpsyt.2013.00141.
[10] White WL. Slaying the dragon: the history of addiction treatment and recovery in America. Bloomington, IL, US: Chestnut Health Systems/Lighthouse Institute; 1998.
[11] Courtwright DT. The NIDA brain disease paradigm: history, resistance and spinoffs. BioSocieties 2010;5(1):137–47. https://doi.org/10.1057/biosoc.2009.3.
[12] Spector S, Parker CW. Morphine: radioimmunoassay. Science 1970 Jun 12;168 (3937):1347–8.
[13] Berkowitz B, Spector S. Evidence for active immunity to morphine in mice. Science 1972 Dec 22;178(4067):1290–2.
[14] Bonese KF, Wainer BH, Fitch FW, Rothberg RM, Schuster CR. Changes in heroin self-administration by a rhesus monkey after morphine immunisation. Nature 1974 Dec 20;252(5485):708–10.
[15] Hill JH, Wainer BH, Fitch FW, Rothberg RM. Delayed clearance of morphine from the circulation of rabbits immunized with morphine-6-hemisuccinate bovine serum albumin. J Immunol 1975 Apr;114(4):1363–8.
[16] Moreno AY, Janda KD. Immunopharmacotherapy: vaccination strategies as a treatment for drug abuse and dependence. Pharmacol Biochem Behav 2009 Apr;92(2):199–205. https://doi.org/10.1016/j.pbb.2009.01.015.
[17] Shen XY, Orson FM, Kosten TR. Vaccines against drug abuse. Clin Pharmacol Ther 2012 Jan;91(1):60–70. https://doi.org/10.1038/clpt.2011.281.
[18] Vocci FJ, Chiang CN. Vaccines against nicotine: how effective are they likely to be in preventing smoking? CNS Drugs 2001;15(7):505–14. https://doi.org/10.2165/00023210-200115070-00001.
[19] Pentel PR, Malin DH, Ennifar S, Hieda Y, Keyler DE, Lake JR, et al. A nicotine conjugate vaccine reduces nicotine distribution to brain and attenuates its behavioral and cardiovascular effects in rats. Pharmacol Biochem Behav 2000 Jan 1;65(1):191–8. https://doi.org/10.1016/S0091-3057(99)00206-3.
[20] Heekin RD, Shorter D, Kosten TR. Current status and future prospects for the development of substance abuse vaccines. Expert Rev Vaccines 2017 Nov;16 (11):1067–77. https://doi.org/10.1080/14760584.2017.1378577.
[21] van Schayck OC, Horstman K, Vuurman E, de Wert G, Kotz D. Nicotine vaccination–does it have a future? Addiction 2014 Aug;109(8):1223–5. https://doi.org/10.1111/add.12569.
[22] Desai RI, Bergman J. Effects of the nanoparticle-based vaccine, SEL-068, on nicotine discrimination in squirrel monkeys. Neuropsychopharmacology 2015 Aug;40(9):2207–16. https://doi.org/10.1038/npp.2015.64.
[23] Hu Y, Smith D, Frazier E, Hoerle R, Ehrich M, Zhang C. The next-generation nicotine vaccine: a novel and potent hybrid nanoparticle-based nicotine vaccine. Biomaterials 2016 Nov;106:228–39. https://doi.org/10.1016/j.biomaterials.2016.08.028.

[24] Carrera MR, Ashley JA, Parsons LH, Wirsching P, Koob GF, Janda KD. Suppression of psychoactive effects of cocaine by active immunization. Nature 1995;378(6558):727–30. https://doi.org/10.1038/378727a0.
[25] Fox BS. Development of a therapeutic vaccine for the treatment of cocaine addiction. Drug Alcohol Depend 1997 Dec 15;48(3):153–8. https://doi.org/10.1016/S0376-8716(97)00121-X.
[26] Martell BA, Mitchell E, Poling J, Gonsai K, Kosten TR. Vaccine pharmacotherapy for the treatment of cocaine dependence. Biol Psychiatry 2005 Jul 15;58(2):158–64. https://doi.org/10.1016/j.biopsych.2005.04.032.
[27] Kosten TR, Domingo CB, Shorter D, Orson F, Green C, Somoza E, et al. Vaccine for cocaine dependence: a randomized double-blind placebo-controlled efficacy trial. Drug Alcohol Depend 2014 Jul;1(140):42–7. https://doi.org/10.1016/j.drugalcdep.2014.04.003.
[28] Evans SM, Foltin RW, Hicks MJ, Rosenberg JB, De BP, Janda KD, et al. Efficacy of an adenovirus-based anti-cocaine vaccine to reduce cocaine self-administration and reacqusition using a choice procedure in rhesus macaques. Pharmacol Biochem Behav. 2016;150–151:76–86. https://doi.org/10.1016/j.pbb.2016.09.008.
[29] Cornell Weill press release Anti-Cocaine vaccine approved for clinical study in humans' https://news.weill.cornell.edu/news/2016/08/anti-cocaine-vaccine-approved-for-clinical-study-in-humans (accessed 27 October 2017).
[30] Choi J, Kim C, Choi MJ. Immunological analysis of methamphetamine antibody and its use for the detection of methamphetamine by capillary electrophoresis with laser-induced fluorescence. J Chromatogr B Biomed Sci Appl 1998 Feb 13;705(2):277–82. https://doi.org/10.1016/S0378-4347(97)00527-6.
[31] Stevens MW, Gunnell MG, Tawney R, Owens SM. Optimization of a methamphetamine conjugate vaccine for antibody production in mice. Int Immunopharmacol 2016 Jun;35:137–41. https://doi.org/10.1016/j.intimp.2016.03.028.
[32] Arora R, Haile CN, Kosten TA, Wu Y, Ramakrishnan M, Hawkins LD, et al. Preclinical efficacy of an anti-methamphetamine vaccine using E6020 adjuvant. Am J Addict 2019 Feb;28(2):119–26. https://doi.org/10.1111/ajad.12867.
[33] Anton B, Leff P. A novel bivalent morphine/heroin vaccine that prevents relapse to heroin addiction in rodents. Vaccine 2006 Apr 12;24(16):3232–40. https://doi.org/10.1016/j.vaccine.2006.01.047.
[34] Stowe GN, Vendruscolo LF, Edwards S, Schlosburg JE, Misra KK, Schulteis G, et al. A vaccine strategy that induces protective immunity against heroin. J Med Chem 2011 Jul 28;54(14):5195–204. https://doi.org/10.1021/jm200461m.
[35] Bremer PT, Schlosburg JE, Banks ML, Steele FF, Zhou B, Poklis JL, et al. Development of a clinically viable heroin vaccine. J Am Chem Soc 2017 Jun 28;139(25):8601–11. https://doi.org/10.1021/jacs.7b03334.
[36] Brady KT, McCauley JL, Back SE. Prescription opioid misuse, abuse, and treatment in the United States: an update. Am J Psychiatry 2016 Jan;173(1):18–26. https://doi.org/10.1176/appi.ajp.2015.15020262.
[37] Bremer PT, Kimishima A, Schlosburg JE, Zhou B, Collins KC, Janda KD. Combatting synthetic designer opioids: a conjugate vaccine ablates lethal doses of fentanyl class drugs. Angew Chem Int Ed Engl 2016 Mar 7;55(11):3772–5. https://doi.org/10.1002/anie.201511654.
[38] Raleigh MD, Peterson SJ, Laudenbach M, Baruffaldi F, Carroll FI, Comer SD, et al. Safety and efficacy of an oxycodone vaccine: Addressing some of the unique considerations posed by opioid abuse. PLoS One 2017;12(12):12. https://doi.org/10.1371/journal.pone.0184876.
[39] Banks ML, Olson ME, Janda KD. Immunopharmacotherapies for Treating Opioid Use Disorder. Trends Pharmacol Sci 2018 Nov;39(11):908–11. https://doi.org/10.1016/j.tips.2018.08.001.
[40] Janero DR. Medications development for substance-use disorders: contextual influences (dis)incentivizing pharmaceutical-industry positioning. Expert Opin Drug Discov 2014 Nov;9(11):1265–79. https://doi.org/10.1517/17460441.2014.951631.
[41] Volkow ND, Collins FS. The role of science in the opioid crisis. N Engl J Med 2017 Nov 2;377(18):1798. https://doi.org/10.1056/NEJMsr1706626.
[42] Volkow ND, Koob G. Brain disease model of addiction: why is it so controversial? Lancet Psychiatry 2015 Aug;2(8):677–9. https://doi.org/10.1016/S2215-0366(15)00236-9.
[43] Kolodny A, Courtwright DT, Hwang CS, Kreiner P, Eadie JL, Clark TW, et al. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. Ann Rev Publ Health 2015;36:559–74. https://doi.org/10.1146/annurev-publhealth-031914-122957.
[44] Burris S. Where next for opioids and the law? Despair, harm reduction, lawsuits, and regulatory reform. Public Health Rep 2018;133(1):29–33. https://doi.org/10.1177/0033354917743500.
[45] Zalewska-Kaszubska J. Is immunotherapy an opportunity for effective treatment of drug addiction? Vaccine 2015 Nov 27;33(48):6545–51. https://doi.org/10.1016/j.vaccine.2015.09.079.
[46] Council of Europe Experts Committee on Ethical Issues and Professional Standards, Ethical questions raised by immunotherapy of addiction. The example of the 'vaccine' against cocaine. <https://rm.coe.int/publication-ethical-questions-raised-by-immunotherapy-of-addiction-the/16807461242010> (accessed 31 October 2017).
[47] Olson ME, Janda KD. Vaccines to combat the opioid crisis: Vaccines that prevent opioids and other substances of abuse from entering the brain could effectively treat addiction and abuse. EMBO Rep 2018 Jan;19(1):5–9. https://doi.org/10.15252/embr.201745322.
[48] Cohen PJ. Immunization for prevention and treatment of cocaine abuse: legal and ethical implications. Drug Alcohol Depend 1997 Dec 15;48(3):167–74. https://doi.org/10.1016/S0376-8716(97)00075-6.
[49] Gartner CE, Carter A, Partridge B. What are the public policy implications of a neurobiological view of addiction? Addiction 2012 Jul;107(7):1199–200. https://doi.org/10.1111/j.1360-0443.2012.03812.x.
[50] Hall W, Gartner C. Ethical and policy issues in using vaccines to treat and prevent cocaine and nicotine dependence. Curr Opin Psychiatry 2011 May;24(3):191–6. https://doi.org/10.1097/YCO.0b013e328345922b.
[51] Carfora A, Cassandro P, Feola A, La Sala F, Petrella R, Borriello R. Ethical Implications in vaccine pharmacotherapy for treatment and prevention of drug of abuse dependence. J Bioeth Inq 2018 Mar;15(1):45–55. https://doi.org/10.1007/s11673-017-9834-5.
[52] Young MJ, Sisti DA, Rimon-Greenspan H, Schwartz JL, Caplan AL. Immune to addiction: the ethical dimensions of vaccines against substance abuse. Nat Immunol 2012 May 18;13(6):521–4. https://doi.org/10.1038/ni.2321.