Vaccines for Drug Dependence: A Systematic Review of the Literature

OCTAVIAN VASILIU*, DANIEL VASILE**
* University Military Central Emergency Hospital "Dr. Carol Davila" Bucharest
** University of Medicine and Pharmacy "Dr.Carol Davila"
Mircea Vulcanescu Str, no.88, Bucharest
ROMANIA
octavvasiliu@yahoo.com

Abstract: Drug abuse and dependence are serious threats to individual and public health. Drug use has a severe impact over global functionality, quality of life, healthcare costs, academic and professional performances, life expectancy etc. Although the importance of drug related disorders is obvious, very few approved treatments are available. Vaccines have been considered a possible solution due to their theoretical long-lasting effects. Vaccines for cocaine and nicotine dependence reached the phase III of human trials, but the results are not very encouraging. No human trials have been initiated for anti-methamphetamine and anti-opioids vaccines, as they are still in the preclinical phase of development. Problems related to haptens and adjuvants are related to the vaccines' immunogenicity and it seems that only a minority of tested subjects respond with significant levels of antibodies. A powerful motivation for change is also required, since a high dose of drug could overcome the level of circulating antibodies induced by vaccines. In conclusion, the current stage of research is not satisfactory, but there is still hope for the future development of anti-drugs of abuse vaccines.

Key-Words: vaccines, drug dependence, drug abuse, drug addiction, haptens, cocaine, nicotine, methamphetamine, opioids

1 Introduction

Drug-induced disorders represent a major challenge for public health due to a large number of negative consequences, d.e. high rates of somatic complications, lower rate of survival, lower quality of life etc. [1,2]. These disorders are being diagnosed frequently in adolescents and young persons, a phenomenon which creates individual health and functional problems, but also creates problems for society, due to the increases in healthcare costs and professional/academic lower performances in a very active population. The recreational use of illicit drugs has also been associated with sudden death, and various substances like cocaine, amphetamines and even marijuana may induce this outcome [3].

Many treatments have been recommended for drug induced disorders, but the problem of long-term efficacy is yet far from being solved. Only for alcohol, opioids and nicotine there are available psychopharmacologic approaches, while for psychostimulants, inhalants, phencicylidine, hallucinogenic drugs there are no approved treatments.

The use of immunotherapy is considered a possible solution to the drug dependence, but the results of studies conducted until now are not very encouraging. Many trials have been conducted on animals, but only a few on humans [4].

There are several problems identified by reviews of trials dedicated to anti-drugs of abuse vaccines. The role of adjuvants is very important for the induction of high and prolonged levels of antibodies, still debates about what adjuvants can be transferred from animal studies to human trials are actual [5]. Another problem is the possibility of overcoming antibody level with higher drug doses, so the vaccine should be accompanied by a form of psychotherapy and enough motivation to discontinue drug use [6]. Haptened vaccines share a common feature, that only one third of the vaccinated subjects get a sufficiently antibody titre enables them to effectively block drug abuse [7].

2 Objective

To evaluate the available data regarding the efficacy of anti-drugs of abuse vaccines in humans and to compare the conclusions of the detected randomized trials.

The secondary objective was to find relevant data regarding possible anti-drugs of abuse vaccines in preclinical stages of development.

3 Methods

A search of major electronic databases (Cochrane, PubMed, PsychInfo, EMBASE, CINAHL) was performed, using key words “cocaine”, “opioids”, “methamphetamine”, “nicotine”, “drug of abuse”, “psychoactive drugs” plus “vaccine”, “immunotherapy” and “biological therapies”.

We included only randomized controlled trials for the main analysis.

For the secondary analysis, of the preclinical trials, we included both trials and reviews of literature.

All papers found between 1990 and 2017 were included in the analyses.

We excluded trials without a specified design, researches without well-defined variables and those with no specified statistical methods.

4 Results

A number of 6 randomized controlled trials have been retained in the analysis for anti-cocaine vaccines, and 8 studies for anti-nicotine vaccines.

Very few studies for other anti-drugs of abuse vaccine have been detected in the literature, and all of them were about preclinical tests. We cited the most relevant sources of information in the secondary analysis, for anti-methamphetamine and anti-opioids vaccines.

4.1. Vaccines for cocaine dependence

The interest for an anti-cocaine vaccine is acute, since no treatment has been proven efficient for cocaine related disorders. A number of vaccines designed to treat cocaine dependence are currently in phase II or III of clinical research. Because cocaine is a small molecule, one of its active metabolites, nor-cocaine, must be conjugated with a immunogenetic protein, cholera toxin B.

Table 1. Anti-cocaine vaccine focused clinical trials

Authors	Methods (variables, design)	Results
Kosten TR, Domingo CB, Shorter D et al. [8]	6-site, 24-week, phase III, double-blind, placebo-controlled RCT; Efficacy of succinyl-norcocaine conjugated to cholera toxin B as a vaccine for cocaine dependence; Urine cocaine metabolites as the main outcome; N=300	No difference between the 3 groups (placebo, high IgG, low IgG) in the main outcome; 29 SAE, but not related to withdrawal or deaths; After 8 weeks more vaccinated than placebo subjects attained abstinence for at least 2 weeks, and the high IgG group had the most cocaine-free urines for the last 2 weeks of treatment, but neither were significant
Orson FM, Rossen RD, Shen X et al. [9]	Phase IIb double-blind, placebo-controlled RCT; Investigational product =cholera-toxin-B (CTB) as carrier protein; Isotype specific ELISAs for determination of IgG and IgM anti-cocaine and anti-CTB antibodies; N=55	Before immunization 36/55 subjects had IgM to cocaine, and after immunization IgG anti-CTB responses were reduced in patients who presented high IgM levels. Subjects who developed an IgM response to cocaine during repeated recreational exposure to cocaine are significantly less likely to produce high levels of IgG from the cocaine-conjugated

		vaccine, probably via type 2 T-cell independent immune response. Therefore, such subjects are poor candidates for the currently tested vaccine.
Nielsen DA, Hamon SC, Kosten TR [10]	16-week, Phase IIb double-blind, placebo-controlled RCT; 5 vaccinations over the first 12 weeks; Main outcome is to verify whether rs647397 variant of the OPRK1 gene influences the response to cocaine vaccine; N=114	Opioid kappa receptor (OPKR) type 1 genotype could be useful for identifying a subset of subjects for whom the cocaine vaccine may be effective. Protective A allele of rs6473797 had a higher drop in the rate of positive urine for cocaine than subjects with risk allele G
Martell BA, Orson FM, Poling J et al. [11]	24-week, phase IIb, double-blind, placebo-controlled RCT plus follow-up at week 24; Immunogenicity, safety and efficacy of a cocaine vaccine; Main outcome-urinary cocaine metabolites levels; N=115	Subjects who reached serum IgG anticocaine antibody levels of 43 μg/mL or higher had significantly more cocaine-free urine samples than those with levels less than this value, and than placebo.
		No SAE was reported.
Martell BA, Mitchell E, Poling J et al. [12]	Open-label, 14-week, dose escalation: Safety, immunogenicity, and clinical efficacy of TA-CD cocaine vaccine; Main outcome-urine toxicology and cocaine antibody; N=18 (16 completers)	2000 μg TA-CD dose group had a significantly higher mean antibody titer response, as compared to 400 μg. Attenuation of cocaine's usual euphoric effects at 6 month follow-up. No SAE was recorded.
Kosten TR, Rosen M, Bond J et al. [13]	Double-blind, placebo-controlled RCT, phase I; Immunogenicity and safety of a therapeutic cocaine vaccine (TA-CD); N=34	Antibody levels were corelated with vaccine dose and number of injections. Anti-cocaine antibodies were detected after second injection, peaked at 3 months and declined to baseline after one year. No SAE was reported.

RCT= randomized controlled trial; SAE= serious adverse event

All trials detected were phase I, II and III, but the results are in general disappointing. An immune response is detected after various doses of vaccine, but the correlation between antibodies levels and cocaine abstinence rates has not reached the significance level in all the trials. Vaccines were generally well tolerated, with no remarkable serious adverse events being reported. A clinical trial detected that OPKR1 genotype could be useful for identifying a subset of subjects for whom the cocaine vaccine may be effective 10].

4.2. Anti-nicotine vaccines

A large quantity of research has been devoted to the validation of anti-nicotine vaccines in smoking population. A number of 7 well designed clinical trials were found, and no strong correlation could be established between antibodies levels and clinical efficacy. Vaccines have been well tolerated, without serious adverse events being reported.

Table 2. Anti-nicotine vaccines focused clinical trials

Authors	Methods (variables, design)	Results
Havermans A, Vuurman EF, van der Hurk et al. [14]	Placebo-controlled parallel-group, repeated-measures design RCT; Investigational product= 3'-aminomethyl-nicotine Pseudomonas aeruginosa r-Exoprotein-conjugated vaccine; Main outcome= reaction-times at n-back task N=48 male smokers	No significant differences related to immunization were detected on brain activity in response to a nicotine challenge.
Hoogsteder PH, Kotz D, van Spiegel PI et al. [15,16]	Placebo-controlled RCT; NicVAX+vareniclin e&behavioural support vs. placebo+varenicline & behavioural support; Main outcome=prolonged CO-validated abstinence; N=558 smokers	No difference in abstinence rates between NicVAX and placebo from wks 9 to 52, or wks 37-52. The top 30% antibody responders, compared to the placebo group, showed a non-significant tendency towards higher abstinence rates from wks 37-52.
Tonstad S, Heggen E, Giljam H et al. [17]	Double-blind, parallel-group RCT, 1-year, 16 visits+16 telephone calls; Nicotine vaccine (Niccine) 40 μg vs. placebo; Main outcomes=exhaled levels of CO, time to relapse, abstinence, withdrawal, smoking reinforcement; N=355 cigarette smokers	At 1-year non-relapse rate was 43.3% in vaccine treated group vs. 51.1% placebo. No benefit of Niccine on smoking status at 6 or 9 months; nicotine antibodies levels increased in the vaccine treated subjects, but no relation with the relapse could be detected.
Hatsukami DK, Jorenby DE, Gonzales D et al. [18]	Double-blind, placebo-controlled multicentre, 6-month RCT; NicVAX 200 μg vs. 400 μg vs. placebo; N=301 smokers	Subjects with the highest serum anti-nicotine Ab response were significantly more likely than placebo-recipients to obtain 8 weeks of continuous abstinence. The 400 μg dose regimen elicited the greatest Ab response and resulted in significantly higher abstinence rates than placebo.
Comuz J, Zwahlen S, Jungi WF et al. [19]	6-month, double-blind, phase II RCT, and 6-month follow-up; Investigational product=Nicotine-Qbeta; N=341 smokers	Well tolerated, highly immunogenic, 100% antibody responder rate after the first injection. Abstinence rate at 2 months was statistically different ($p<0.05$). Continuous abstinence between months 2 and 6 was not significantly different, except for those

		with highest antibody levels (difference maintained at 12 months follow-up).
Wagena EJ, de Vos A, Horwith G, van Schayck CP [20]	Phase 1/2 placebo-controlled RCT; Safety and immunogenicity of nicotine vaccine in smokers and non-smokers; Investigational product= purified 3'-aminomethyl-nicotine conjugated with detoxified Pseudomonas aeruginosa r-Exoprotein A; N=30	Vaccine was well tolerated up to 266 days. Significant increases in levels of nicotine-specific antibodies were detected from 7 days after the second vaccination (day 21), and reached nicotine-specific antibody levels at day 49.
Hatsukami DK, Rennard S, Jorenby D et al. [21]	Placebo-controlled RCT; NicVAX 50, 100, 200μg vs. placebo; N=68 smokers	Safe and well tolerated. Vaccine immunogenicity was dose-related. The 30-day abstinence rate was significantly different across the doses, the highest rate of abstinence was reached by subjects receiving 200 μg.

4.3. Other vaccines focused on drug dependence

Methamphetamine addiction is a serious health problem and vaccines designed for this disorder have been tested in animal models [22]. Anti-opioids vaccines have also been created especially for blocking lethal overdoses, yet studies on humans are not ongoing [23]. A conjugated vaccine for a wide panel of fentanyl analogues has been designed and tested on animal models with good results [24].

4.4. Results discussion

There is a marked discrepancy between the expectations and reality in the field of anti-drug vaccines. While vaccines are considered a sort of "golden bullet" that will target the circulating drugs of abuse and annihilate them on the spot, reality is far more complicated. Finding tolerated haptens, and obtaining sufficient titres of antibodies are the main challenges detected by this review.

The current stage of research is relatively advanced for anti-nicotine and anti-cocaine vaccines, although no product obtained yet the approval of a drug-regulatory agency.

5 Conclusion

This review is considered necessary because the general interest for the field of vaccines not only for drug dependence, but also for other psychiatric disorders, like Alzheimer dementia, increased in the last century, and many clinical trials focused on this topic are ongoing.

The advance in anti-drugs of abuse vaccines research is very slow, and the results are yet inconclusive. Many challenges are still to be solved, regarding the level of vaccines immunogenicity. The overall tolerability of the tested vaccines is good, with very few adverse events being reported in clinical trials. Only anti-cocaine and anti-nicotine vaccines have reached the level of human trial development, with mixed results.

Further basic research should target the quality of haptens, and the clinical trials should include the monitorization of the antibodies titers on longer periods, to establish their stability. Vaccines for a wider range of drugs should be tested, as patients usually consume more than one drug at a time, and they could be addicted to multiple drugs concomitantly.

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