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Review Article

Current status of vaccines for substance use disorders: A brief review of human studies

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ABSTRACT

Substance use is a major public health concern worldwide. In the United States, drug-related deaths have increased many-fold in the past two decades due to the infiltration of more potent and lethal drugs such as fentanyl. Despite significant advancement in medicine, the management of substance use disorders (SUD) continues to be fraught with high attrition, relapse, morbidity, and mortality. The conceptual transition of a SUD from a moral failing to a chronic disease caused by substances facilitated the expansion of biological treatments, including pharmacotherapy, neurostimulation, and immunotherapy. While the quest for vaccines against drugs of abuse had an optimistic start in animal models, clinical trials in humans have yielded disappointing results. This paper provides a brief review on the current progress of vaccines against nicotine, stimulants (cocaine and methamphetamine), opioids including fentanyl, novel psychoactive substances (synthetic cathinones and synthetic cannabis), and discusses prospects for vaccine technology in the treatment of SUD.

1. Introduction

Over a century ago, the creation of the first vaccine for smallpox led to the development of preventative interventions for multiple illnesses. The success of vaccination is exhibited by the significant drop in morbidity and mortality against various pathogens, some of which have been virtually eradicated. Not surprisingly, scientists would attempt to apply this body of research in immunology to other potentially preventable conditions.

The conceptualization of substance use disorders (SUD) as a brain disease caused by toxins inspired efforts to develop vaccines and other immunotherapies for treatment and prevention of SUD. According to the National Survey on Drug Use and Health (NSDUH), 20.1 million people age 12 and older met the criteria for a SUD in the United States in 2019 [1]. Of particular concern has been substances adulterated with illicitly manufactured fentanyl that has been the major cause of overdoses from opioids [2]. Moreover, even during the COVID-19 pandemic when the volume of drug screens dropped significantly, those tested showed a marked increase in urine drug screens positive for illicit fentanyl (35%), and more strikingly for methamphetamine (89%), which heralded the fourth wave of the opioid epidemic with combined stimulants and opioids [3]. With the increasing morbidity and mortality from this combination of drugs, which have no effective or FDA approved medications, therapeutic strategies have expanded to include immunization with vaccines, anti-drug monoclonal antibodies, and gene transfer of antidrug proteins. This review will examine the progress in the development of vaccines against drugs of misuse with a primary focus on available human studies.

2. Background

Since their conception in the late 1960s, research into vaccines for addictive substances has provided important insights into substance use disorders and the brain. The idea was to introduce the body to the foreign substance (i.e. cocaine) and induce T-cell and B-cells to make antibodies against the substance. Once the person has antibodies, using the drug would lead to the formation of a drug-antibody complex that is eliminated via phagocytosis or metabolized rather than crossing the blood brain barrier and producing psychoactive effects. The liver is involved in metabolism of the drug or degradation of the drug- antibody complex in lysosomes. A fraction of the unchanged drug or its metabolite is excreted by the kidneys. Some drugs are also eliminated through the digestive tract after release from the antibody. While these antibody complexes would ideally lead to a complete blockade of the drug,

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antibodies may also slow entry of substantial portions into the brain and that delayed time to effect limits the drug's reinforcing properties [4–11].

However, optimistic predictions have been tempered by challenges that arose in each step of the development of anti-addiction vaccines. Since most misused substances are haptens, which are too small to generate an antibody response, they must be conjugated to an immunogenic carrier protein (e.g. cholera toxin, keyhole limpet hemocyanin (KLH), tetanus toxoid (TT)) mixed with an adjuvant such as alum to enhance the immune response. All of these anti-addiction vaccines have struggled to produce sufficient levels of antibodies. Furthermore, even with a high titer of antibody response, only a small percentage of antibodies may have a high affinity for the antigen. For some vaccines, promising results in animal studies did not replicate in human trials. To date, a variety of vaccines have been tested using different combinations of adjuvants and carrier proteins to increase the magnitude, affinity, and durability of antibodies [12–14]. Unfortunately, many failed studies conducted by pharmaceutical companies were never published. Among published studies, data on antibody levels, affinity, and specificity was not available for inclusion in this review.

3. Vaccines

3.1. Nicotine

Tobacco use is a leading cause of morbidity and mortality worldwide. Each year, tobacco-related diseases kill 480,000 Americans and 6 million people globally [15]. An extremely efficient drug delivery device, the cigarette or vaping allows for the rapid occupation of nicotine receptors upon smoking. One puff occupies 1/3 of the receptors and three cigarettes saturate the receptors for approximately 3 h in humans in vivo [16]. Repeated nicotine use leads to long-term neuroadaptations that produce tolerance and cue-induced cravings. It is estimated that over 70% of people want to quit, 40% try to quit each year, but <3% are successful without treatment [17]. The rise of electronic cigarette use has also surged among adolescents, more than doubling from 2017 to 2019 [18]. Therefore, the development of effective treatments has been paramount to public health.

First-generation nicotine vaccines included NicVax (3′-aminomethyl-nicotine conjugated to detoxified pseudomonas exoprotein A), which demonstrated promising results in a randomized double-blinded, placebo-controlled, multicenter phase II clinical trial with 301 smokers. The trial assessed the efficacy of the vaccine at two different doses (200 μg and 400 μg) for smoking cessation The group receiving the 400 μg dose of the vaccine had high antibody titers and demonstrated significantly higher abstinence rates compared to placebo [19]. However, these optimistic results were not replicated in subsequent trials. In a phase IIb randomized, placebo-controlled trial, six doses of NicVax at 400 μg were administered with 12 weeks of varenicline ($N = 278$) and tested against a placebo ($N = 280$) to assess for smoking cessation and relapse prevention. Outcomes measured from weeks 9 to 52 showed no significant difference in abstinence rates between NicVax and placebo [20]. Two phase III clinical trials for NicVax have since been conducted and neither yielded significant results compared to placebo [21,22]. Follow-up neuroimaging studies examined the effects of the vaccine on the brain. One study ($N = 11$) using single-photon-emission topography (SPECT) showed a 12.5% reduction in nicotine binding to β2-containing nicotinic acetylcholine receptors in those receiving four doses of NicVax 400 μg [23]. However, a larger randomized, placebo, controlled trial with fMRI did not yield significant effects on brain activity with 5 doses of NicVax 400 μg compared to placebo. The negative fMRI results could have been due to different imaging modalities; SPECT detects receptor occupancy whereas fMRI informs about neural activity based on relative oxygenation of each brain region. Small alterations in receptor occupancy are likely not sufficient to result in functional changes that are detectable on fMRI [24]. Three other nicotine vaccines have been tested in phase II clinical trials: Nic002 (conjugated to virus-like particles (VLP) formed from the protein coat of bacteriophage Qβ), Niccine (conjugated to tetanus toxoid), TA-NIC (conjugated to recombinant cholera toxin B). The results of the TA-NIC vaccine study is not publicly available, but an email with Thomas Kosten, MD (kosten@bcm.edu) in September 2021 revealed that the study failed to show a sufficient response in smoking cessation to merit continuation [25]. Niccine failed to produce significant results whereas Nic002 (also known as NicQb), like NicVax, showed significant abstinence rates only in subjects who generated a robust antibody response. The nicotine vaccines are reviewed in detail by Xu et al. [14,26–28] Altogether, we learned that there is a broad range of antibody responses among individuals and that first-generation nicotine vaccines have struggled to consistently induce sufficient antibody production for efficacy.

The search for an effective nicotine vaccine continues with novel approaches to vaccine design. Keyler et al. demonstrated enhanced immunogenicity with a bivalent nicotine vaccine in rats [29]. Other methods in second-generation vaccine development include synthetic nicotine haptens conjugated to diphtheria toxoid, variations of adjuvants and proteins, and non-immunogenic self-assembling nanoparticles that carry antigens and adjuvants [30,31]. The nanoparticle design is thought to fine-tune the immune response to the antigen and not the carrier protein, which could potentially reduce the number of booster shots needed. Nanoparticle carriers could also activate the immune cascade more effectively because of the efficient drainage of the antigen into lymph nodes. Another vaccine involves a liposome complex conjugated to nicotine, which is thought to improve stability. Some second-generation vaccines have achieved a more consistent and robust antibody response in animal studies and results of phase I human trials are underway [32–35].

Previously disappointing outcomes have not discouraged scientists in the field; rather, the process has provided useful information on how to move forward. For example, researchers gleaned that both high antibody titers and high affinity to the antigen are needed to generate a response and some adjuvants enhance the immune reaction more than others. These insights have refined the process of candidate vaccine selection before proceeding to human trials [30]. As second-generation vaccines make their debut, we will understand how they perform in both efficacy and practical application with consideration of tolerability, cost, and ease of delivery.

3.2. Cocaine

The NSDUH data show that the prevalence of cocaine use has remained stable since 2009 with approximately 977,000 people age 12 and older meeting the criteria for cocaine use disorder in 2018 [36]. Despite a decline from previous years, cocaine remains one of the most widely used drugs in the world. The past two decades (1999–2019) saw a 4-fold increase in overdose deaths involving cocaine adulterated with synthetic opioids other than methadone [2]. While several medications from different classes have been tested, there is no well-established pharmacotherapy for treatment of cocaine use disorder. This clinical need has spurred a strong interest in developing effective treatment strategies, including pharmacotherapy, psychotherapy, psychosocial interventions, and preventative anti-cocaine vaccines.

A 1995 study using the anti-cocaine vaccine GNC-KLH (cocaine hapten GNC conjugated to KLH) reduced levels of cocaine in the brain tissue of immunized rats by 80% compared to controls [37]. Among candidate vaccines developed in subsequent years, only the TA-CD vaccine has completed clinical trials in humans. Comprised of succinyl norcocaine conjugated to cholera toxoid with an aluminum hydroxide adjuvant, the TA-CD vaccine showed promise among the high-antibody group in phase II trials. In a study by Martell et al. with 115 participants in a methadone maintenance program, the high antibody group with levels above 43 μg/mL had a greater proportion of subjects experiencing a greater than 50% reduction in cocaine use and a higher percentage of

cocaine-free urine samples compared to placebo and the low-antibody group. However, there was considerable variability in antibody levels overall, with only 38% of subjects achieving the cutoff IgG level of 43 μg/mL [38]. Kosten et al. conducted a phase III trial with 300 participants recruited from 6 centers across the USA. Subjects were randomized to receive five doses of the TA-CD vaccine or placebo administered over 8 weeks, concurrent with optional cognitive behavioral therapy. Despite 67% of immunized subjects producing high antibody levels (≥42 μg/mL), there was no significant difference in the number of cocaine-positive urine samples compared to placebo and to the low-antibody group at week 16. However, positive findings included a nearly 3-fold higher retention rate in the high-antibody group compared to the low-antibody and placebo groups. The high-antibody group also had a greater odds ratio of having cocaine-free urines and sustained abstinence in the final 2 weeks. One unforeseen finding was that the high antibody group had more cocaine-positive urines compared to the low antibody group throughout the study. The authors posited those adequate responders may have increased cocaine use to override the blockade from the vaccine [39]. The TA-CD vaccine may still have potential in a population of cocaine users highly motivated to stop or reduce use of cocaine, playing a role in relapse prevention rather than initiation of abstinence.

A different cocaine vaccine dAd5GNE has advanced to phase I clinical trials after showing efficacy in animal studies. Made from a third-generation cocaine hapten (GNE) conjugated to a disrupted and inactive serotype 5 adenovirus (dAd5), the dAd5GNE vaccine was shown to reduce cocaine levels in the brain and cocaine-induced locomotor activity and toxicity in mice, even with daily use at high doses [40]. In a study with rhesus monkeys, vaccination significantly reduced reacquisition of cocaine self-administration after extinction, but only 25% of the primates showed a reduced preference for cocaine over candy. Thus, the dAd5GNE may function best as a relapse-prevention strategy in humans [41]. Second-generation cocaine vaccines attempted to increase immunogenicity by conjugating the cocaine hapten to flagellin or to nanofibers, the latter inducing antibodies in mice without adjuvants [42]. Other strategies include using different adjuvants to stimulate toll-like receptors (TLR) and combining the vaccine with cocaine degrading enzymes.

3.3. Methamphetamine

Methamphetamine (MA) use has been on the rise in the United States for the past decade. With potency increasing from 85.4% in 2012 to over 97% in 2019, MA use is responsible for numerous health risks and remains a major public health concern. Drug overdoses from a mixture of opioids and methamphetamine increased over 8-fold between 2012 and 2019 [2,43]. As with cocaine use disorder, there are no pharmacotherapies that have shown reliable effectiveness. While no MA vaccines have advanced to clinical trials in humans, several have shown efficacy in animal models.

Kosten's group developed a MA vaccine comprised of the hapten succinyl methamphetamine (SMA) conjugated to KLH with monophosphoryl lipid A (MPLA) as the adjuvant and showed that it attenuated MA place conditioning in mice [44]. The group conducted further studies using TT attached to SMA mixed with alum and either the TLR4 agonist E6020 or the TLR5 agonist entolimod [45]. Both types of adjuvant combinations reduced acquisition and reinstatement of MA place conditioning in mice. Another vaccine MH6-KLH successfully prevented MA-induced locomotion in rats that received MA via intraperitoneal injection. Interestingly, the vaccine was not effective when MA was administered by vapor inhalation. The authors attributed the negative findings to a 10-fold higher plasma level of MA with inhalation, despite the amount inhaled producing similar locomotor activity to injection [37]. Keller et al. demonstrated efficacy of the vaccine IXT-v100 adjuvanted with glucopyranosyl lipid A (GLA) in attenuation of MA-taking and MA-seeking behaviors in rats [46]. Other groups investigated different MA hapten densities and derivatives mixed with various adjuvants (e.g. GLA, allydrogel) to amplify antibody production [47]. For example, one study concluded that a secondary amine in the MA hapten, a peptide-based linker, and tetanus toxoid are essential for high antibody production [48]. Another promising design using the adjuvant tucaresol, modified and incorporated into liposomes, induced antibodies with greater specificity than with MPLA [49].

An additional focus is to protect against lethal doses of MA. Olson et al. discovered that hapten stereochemistry influences efficacy by comparing enantiomeric and racemic methyl-linked MA haptens conjugated to TT and adjuvanted with CpG ODN 1826 and alum. While all three of these forms of MA haptens: (S), (R), and (R/S) generated antibodies, only the (S) enantiomer of this vaccine significantly protected against lethality [50]. Researchers hope to advance these candidate vaccines to human trials. Similar to second generation nicotine vaccines, designs using nanoparticle carriers is an area of active research [51].

3.4. Opioids

The current opioid crisis began in the 1990s with the introduction of OxyContin by Purdue Pharma and has since undergone three waves. The late 1990s saw a rise in overdose deaths due to prescription opioids, transitioning to heroin overdoses in 2010. The third wave of deaths began in 2013 with illicitly manufactured synthetic opioids, particularly fentanyl and fentanyl analogs that are often found in combination with heroin, counterfeit pills, and stimulants. In 2019, over 36,000 deaths involved synthetic opioids, accounting for nearly 73% of all opioid-related deaths that year. Moreover, overdose deaths due to synthetic opioids accelerated during the COVID-19 pandemic. In the 12 months leading up to May 2020, there was a 38.4% increase in deaths due to synthetic opioids (other than methadone) compared to the previous year [52–54]. As mentioned previously, we are now in a fourth wave of this epidemic with overdoses typically occurring with combinations of fentanyl and the stimulants cocaine or methamphetamine.

The development of opioid vaccines is associated with a variety of specific problems: there are multiple opioid products on the market so the user can switch to a different one not targeted by the vaccine, most opioids have active metabolites, and opioids have a legitimate role in medical treatment and need to remain available for patients. An ideal vaccine would induce antibodies specific to the misused opioids while allowing for medical intervention when necessary. While opioid vaccines have not advanced to clinical trials, some have shown efficacy in animal models. In a study by Kosten et al., the morphine vaccine KLH-6-SM (6-succinylmorphine linked to lysine groups on KLH) attenuated morphine-induced behavioral responses in rats. Vaccinated rats also showed a 25% reduction in brain morphine levels compared to unvaccinated rats [55]. Because heroin rapidly breaks down into the psychoactive metabolites 6-mono-acetylmorphine (6-MAM), morphine, and morphine-6-glucuronide, an effective heroin vaccine also would have to target these compounds. A morphine conjugate vaccine M-KLH reduced 6-MAM concentration in rat brains, which was essential for blocking heroin-induced locomotor activity.12/15/2021 9:36:00 AM The dynamic Her-KLH heroin vaccine creates antibodies against heroin and its metabolites and demonstrated the ability to diminish heroin reward and heroin-induced drug-seeking. While it was not able to prevent cue- or stress-induced relapse, vaccinated rats resumed heroin intake at the level attained before vaccination after a period of abstinence, rather than rapidly escalating intake as observed in non-vaccinated rats. Vaccinated rats also required significantly higher doses of heroin for analgesia. These findings suggest that the Her-KLH vaccine may be particularly effective for relapse prevention and protect from lethal doses of heroin [56]. The OXY-dKLH vaccine against oxycodone prevented oxycodone-induced analgesia and respiratory depression in vaccinated rats with minimal cross-reactivity to methadone, buprenorphine, and opioid antagonists [57].

Of particular interest has been vaccines against fentanyl. The

adulteration of other substances with fentanyl has led to a rapid increase in overdoses among unwitting users. Because fentanyl is many times more potent than morphine (50–100×), the lethal dose is very small at approximately 2 mg. Fentanyl analogs can be up to 10,000× more potent than morphine and are lethal at even smaller doses [58]. Therefore, vaccines against fentanyl may be particularly effective because the concentration of antibodies needed is lower than concentrations needed for blocking other drugs such as cocaine. Fentanyl vaccines tested in rodents and rhesus monkeys have shown promising results for overdose prevention as vaccinated animals required much higher doses of fentanyl for analgesic and respiratory depressant effects [59,60]. A recent study in mice demonstrated a strong blockade of fentanyl-induced analgesia and brain penetration using vaccines with the adjuvants LTA1 and dmLT, which were delivered intranasally and sublingually, respectively. Mucosal vaccinations may have advantages of ease of use for self-administration and to counteract snorting and/or smoking mechanisms of opioid use [61].

Opioid vaccines will likely experience similar challenges as previously mentioned vaccines when administered to humans. Opioid users may compensate for reduced euphoria by increasing the dose or switching to using alternative opioids that could be even more lethal. It is likely that opioid vaccines will be more beneficial as an adjunct to opiate agonist treatment and for overdose protection, particularly protection from fentanyl overdoses, since current agents like methadone and buprenorphine do not block fentanyl. Future studies are anticipated to investigate multivalent vaccines that target different types of opioids [62].

3.5. Novel Psychoactive Substances

Novel psychoactive substances (NPS) refer to a broad range of drugs manufactured in clandestine laboratories that were marketed as legal alternatives to known substances such as amphetamines and cannabis. Synthetic cathinones, commonly referred to as “bath salts,” are chemically related to cathinone found in the khat plant. MDPV (3,4-methylenedioxypyrovalerone) is a cathinone that is 10 times more potent and reinforcing than cocaine [63,64]. Synthetic cannabinoids constitute a large and growing group of substances that had been marketed as legal and inexpensive cannabis prior to their ban along with cathinones by the Synthetic Drug Abuse Prevention Act of 2012 [65]. Use of these substances are associated with numerous health risks, including cardiac arrest, psychosis, seizures, and overdose fatalities [66].

Vaccines targeting cathinone derivatives and synthetic cannabinoids are currently being tested in animals. Nguyen et al. developed vaccines with the cathinone derivatives α-PVP and MDPV conjugated to KLH, which were effective at reducing locomotor activity and self-administration in rats [67]. Another study further supported the efficacy of the MDPV vaccine and expanded on its action by comparing MDPV with cocaine self-administration after vaccination. They found that the vaccine is specific to MDPV, since rats using cocaine did not respond to the MDPV vaccine. The effectiveness of vaccination also appears dependent on the dose of MDPV. At low doses, vaccination appeared to have no effect on MDPV reinforcement, whereas at higher doses, there was a significant reduction in self-administration. Similar to other vaccines, this vaccine was not protective at the highest tested doses of MDPV, which indicates a potential for dose escalation to override the blockade [63]. Regarding synthetic cannabinoids, Lin et al.’s group studied 10 hapten designs conjugated to KLH to determine the optimal vaccine composition that would produce effective antibodies and have broad cross reactivity. They successfully isolated three haptens that had cross reactivity to 5–6 compounds each. A vaccine cocktail consisting of two haptens could target more than 10 synthetic cannabinoids. Most importantly, their vaccines were efficacious at reducing drug effects on locomotion and body temperature in mice. To make relevant to human smoking behavior, both injection and vaping routes of drug administration were tested [68]. These vaccines show promise in animal models and advancement to human studies is still pending.

4. Summary and conclusions

Researchers have made significant progress in vaccine development for SUD, and now have a more comprehensive understanding of vaccine design as well as human behavior after vaccination. Despite the success of several vaccines in animal studies, the ones advancing to human clinical trials (TA-CD and NicVax) failed to demonstrate efficacy against placebo. Even at adequate antibody titers, cocaine users may increase their use to compensate for the blockade, which could lead to toxicity and overdose. These studies showcased the importance of intrinsic personal motivation for abstaining to enable the vaccines to be helpful in reducing use or maintaining abstinence. In addition, clinical trials have been limited by multiple factors such as need for repeated immunizations, which would likely be unappealing to patients in a naturalistic setting. Different routes of drug use like inhalation and subcutaneous injection were not tested in many trials. The introduction of stronger, more lethal substances fuels continued interest and persistence in improving vaccine and experimental designs. As discussed, many vaccines are still in experimental stages using animal models, with some creating vaping and injection scenarios to better mimic human behaviors. Other designs investigate a range of drug doses at which vaccination becomes effective or loses efficacy, which could allow for identification of patients who would benefit from vaccination based on their level of use. For some substances such as fentanyl and its derivatives, the objective has changed from inducing abstinence to minimizing toxicity and overdose prevention. Overall, vaccines may be most beneficial as an additional tool rather than a stand-alone treatment.

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