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REVIEW

A Review of Immunotherapeutic Approaches for Substance Use Disorders: Current Status and Future Prospects

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Abstract: Substance use disorders (SUDs) have been a major public health challenge for decades and continue to cause significant morbidity and mortality worldwide. Due to limitations in pharmacologic treatment options, there remains a significant need for the development of novel immunotherapeutic approaches. In this review, we discuss the therapeutic potential of vaccines for SUDs. Although early preclinical animal studies were optimistic and successful, few vaccines have reached human clinical trials. Only nicotine and cocaine vaccines have successfully advanced to Phase 3 clinical trials and neither are currently available as a treatment option. Various innovative approaches in vaccine design have been made to overcome limitations and improve immunogenicity, including the use of nanoparticles, synthetic haptens, and more immunogenic adjuvants. While success has thus far been elusive, with substantial scientific advancements in vaccine technology, immunotherapy remains a promising and viable option for the treatment of SUDs.

Keywords: substance use disorder, vaccines, nicotine, opioid, cocaine, methamphetamine

Introduction

Two centuries have passed since Edward Jenner first inoculated an 8-year-old boy with cowpox using active pustules from a cowpox patient on May 14, 1796,[1] and scientific advances in immunotherapeutic approaches continue. With the most recent humanitarian disaster, the COVID-19 pandemic, the importance of vaccines was highlighted once again.

Substance use disorders (SUDs) are characterized by a clinically significant impairment in health and social function and loss of control over use despite adverse consequences.[2] SUDs are a rapidly growing public health concern worldwide. Based on data from the National Survey on Drug Use and Health (NSDUH), approximately 14.5% of individuals 12 years or older in the US met criteria for a SUD.[3] Based on data from the 2021 world drug report, 36 million people worldwide were affected by drug use disorders in 2019—an increase of 9 million from the estimate in 2010. Despite this increase, the availability of treatment options is limited.[4] Could vaccines play a role?

The first use of drug-specific antibodies as a therapeutic agent was in an animal study in the 1970s which consisted of using a morphine–bovine serum albumin (BSA) conjugate to attenuate heroin self-administration in a rhesus monkey.[5] Current immunotherapeutic approaches for SUDs mainly include active immunization with vaccines, anti-drug monoclonal antibodies (mAb), catalytically efficient metabolic enzymes, and gene transfer of anti-drug proteins, including mAb.[6] Vaccines are able to generate high-affinity anti-drug IgG antibodies that neutralize and prevent the drug from acting on its receptor sites in the brain.[6] Conjugate vaccines have been shown to be effective in producing promising physiological and behavioral results in pre-clinical and clinical studies.[6] In the production of the anti-drug vaccine, a chemical linker is being used to generate a hapten.[7] This is primarily due to the small molecule drugs' inability to create immunogenicity. Coupling the hapten with a carrier protein produces a drug immunoconjugate preserving the chemical structure of the drug. With the formulation of the immunoconjugate with adjuvants, the anti-drug vaccine production ends.[7] Due to its ability to induce T-helper (Th)2-type

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immunity, which favors drug-neutralizing IgG antibody production as a result of CD4 T cell dependent B cell activation and cost-effectiveness, alum is considered an ideal adjuvant.[7,8] Moreover, to target innate immunity, molecules called pathogen-associated molecular patterns (PAMPs) are added to alum to target innate immune receptors and increase the vaccine's immunogenicity.[7] PAMPs can be found in infectious bacteria and viruses and activate pattern recognition receptors (PRRs) to stimulate D.C. and B cell maturation.[9] Among several distinct classes of PRRs, toll-like receptors (TLRs) are widely targeted as they induce a long-lasting immune response.[7,9] Currently, the only FDA-approved TLR adjuvant is Monophosphoryl lipid A (MPLA), a clinically utilized TLR-4 agonist.[9] As a successful example, addition of TLR9 (CpG ODN 1826) to the original alum adjuvant in a heroin vaccine trial has enhanced anti-drug antibody responses significantly.[10] In another cocaine vaccine study, to explore ways to increase the vaccine's efficacy, the bacterial protein flagellin was investigated. Using flagellin as a carrier and adjuvant stimulated antibody production in a dose-dependent manner.[10]

Different methods have been used to evaluate the efficacy of vaccines. One method is to use the enzyme-linked immunosorbent assay (ELISA) for quantifying the antibody titer produced in response to vaccines.[11] On the other hand, radioimmunoassay (RIA) directly measures drug interactions with tracers by deploying isotopically labeled drug tracers.[11] As an alternative, liquid chromatography with mass spectrometry (LCMS) can detect drug metabolites and quantify the antibody-bound drugs.[12] LCMS has mainly been used in studies on drugs with an extremely short half-life and rapid metabolization like heroin.[12] As a result of concerns regarding accuracy of ELISA in detecting antibody affinity in rapidly metabolized substances, a nonradioactive method using labeled drug tracers and equilibrium dialysis (ED) coupled with ultra-performance liquid chromatography tandem mass spectrometry (UPLC/MS/MS) to assess the accurate binding affinities of heroin hapten antibodies to 6-AM and morphine has been developed.[11] Other alternatives are surface plasmon resonance (SPR) based methods which deploy optical measurement based on reflection by a surface coated with a fine layer of metal for detection of antigen-specific IgG for differentiating the antibody responses.[13,14] A more recent approach without a requirement for sample preparation and immobilization and a shorter dialysis time includes using equilibrium dialysis (ED)-based approach coupled with fluorimetry (ED- fluorimetry) to measure the antibody binding-site concentration to the ligand in an aqueous environment.[15]

Furthermore, behavioral models have been deployed to evaluate the pharmacodynamics of drug vaccines.[7] For example, the antinociceptive effects of opioids can be measured using different noxious stimuli.[7] Additionally, locomotor activity measurement can be done via infrared photo beam, tracking systems, and drug self-administration behavior.[7]

Overall, limitations in current therapeutic options for SUDs coupled with the emerging and evolving landscape of synthetic and designer drugs highlight the need for additional treatment options. A better understanding of the future prospects and challenges will be possible by depicting a clear picture of what is being done in this field and the current status of immunotherapeutics. Our review aims to critically and comprehensively examine the current state and future potential role of immunotherapies in the treatment and prevention of SUDs. See Table 1 for a summary of discussed immunotherapeutics in this review.

Vaccines for Substance Use Disorders

Opioids

Opioid use disorder (OUD) is a pattern of opioid use leading to clinically significant impairment or distress which causes intense cravings that lead to compulsive drug seeking and use despite harmful consequences.[2,16] Examples of opioids include morphine, heroin, codeine, fentanyl, oxycodone, and others. OUD affects over 2.1 million people in the United States and causes over 120,000 deaths worldwide annually.[17] Additionally, synthetic opioids such as fentanyl are believed to have caused nearly 30,000 of the 50,000 deaths involving opioids annually in the US due to their high potency.[18] Medications for OUD revolve around mu-opioid receptor antagonist naltrexone, mu receptor partial agonist buprenorphine, and mu receptor full agonist methadone.[19]

Oxycodone: The only opioid vaccine to reach a clinical trial is an oxycodone vaccine, Oxy(Gly)4-sKLH. This vaccine was developed by modifying oxycodone and conjugating it to a carrier protein through a tetraglycine linker. It was then conjugated with a covalent amide bond to the keyhole limpet hemocyanin (KLH) carrier protein.[20] The long-term goal of the study is to assess the safety and effectiveness of the Oxy(Gly)4-sKLH vaccine in reducing the abuse of opioids through a self-reported measure of "drug liking".[21] The researchers aim to develop a combined vaccine against

Table 1 Summary of Discussed Immunotherapeutics

Drug	Clinical Trials	Pre-Clinical Animal Studies
Oxycodone	**Oxy(Gly)4-sKLH** Phase 1/2: Still ongoing with an estimated completion date of December 30, 2023.[21]	**Oxy-TT** %50 lower oxycodone brain concentrations in Oxy-TT rats compared to TT rats.[22]
Heroin		**Her–KLH, Mor-KLH** Effective blockade of drug activity and prevention of the drug abuse in rats.[25] **Heroin-HIV-1 (H2) vaccine**High endpoint titers and attenuation in heroin induced antinociception and hyperlocomotion.[27]
Morphine		**KLH-6-SM** Production of anti-morphine antibodies and decreased behavioral effects, and a 25% decrease in brain levels of morphine in rats.[28] **M(Gly)4-KLH** High retention of all three opioids in plasma compared to controls and lower heroin-induced locomotor activity in rats.[26]
Fentanyl		**FEN-CRM** Blockade of drug-related analgesia and decreased CNS penetration of drug in mice.[31] **Fentanyl-TT** Up to 33-fold anti-nociceptive potency shift and significant protection from lethal fentanyl doses in mice.[32] 22-fold potency shift in fentanyl vs food choice, and a significantly blunted fentanyl reinforcement in rats[33] Significant potency shifts in fentanyl's behavioral effects and a substantial change of fentanyl potency to produce antinociception in rhesus monkeys.[34]
Nicotine	**NicVax** Phase 3: Ineffective in increasing abstinence.[42] Phase 2: 12.5% reduction in nicotine binding to b2*-nAChRs in the brain.[43] **TA-NIC** Phase 1: Abstinence in 38% of the vaccine group compared to 8% in the placebo group.[45] Phase 2: No results published.[46] **Nic-Qb (NIC002)** Phase 1: Production of nicotine-specific Ig G and Ig M antibodies in day 7 and 14.[48] Phase2b: abstinence rates were 20.2% higher in vaccine group compared to placebo.[47] **SEL-068** Phase 1: No results reported.[50] **Niccine** Phase 2: Higher nicotine antibody levels in vaccine group. However, nonsignificant difference in relapse rates between two different groups.[51] **NIC7-001, NIC7-003** Phase 1: No results published.[53]	**Nic-Qb (NIC002)** Higher levels of antibody and reduced nicotine levels in brain of mice.[48] **SEL-068** Dose dependent inducing effects on antinicotine antibodies in male squirrel monkeys.[49] **NIC7-001, NIC7-003** Generation of anti-nicotine antibodies in primates.[52] **Nic311** Lower brain levels of nicotine and reduced locomotor activity in rats.[54]

(*Continued*)

Table 1 (Continued).

Drug	Clinical Trials	Pre-Clinical Animal Studies
Cocaine	**TA-CD** Phase 2: Clinically significant relationship between attaining high anti-cocaine antibody levels and reduced cocaine use.[54] Phase 3: Clinically unsignificant difference in abstinence rate between placebo and vaccine group.[57] **dAd5GNE** Phase 1: still ongoing with an estimated completion date of December 2025[64] **TV-1380** Phase2: Dose dependent increase in abstinence rates between placebo and vaccine group.[63] **RBP-8000** Phase 2: Up to 90% decrease in plasma concentration and in physiological effects of cocaine in intervention group.[62]	**dAd5GNE** Reduced cocaine occupancy in the brain of primates.[59] Mitigation in the effects of cocaine in different organs in primates.[60] **TV-1380** Decrease in intoxicating effects of cocaine and drug seeking behavior in rats.[66] **RBP-8000** Three times faster elimination of cocaine from rhesus-monkeys brain intervention group.[67] **GNCgzk IgG** prevention of acute toxicity and lethality of cocaine in mice.[72] **AAVrh.10 antiCoc.Mab** sequestration of cocaine in the blood and reduced cocaine-induced behavioral effects in mice.[73]
Methamphetamine	**Anti-METH mAb7F9 (ch-mAb7F9(IXT-m200))** Phase 1: No results published.[81] Phase 1/2: Results pending.[82]	**MH6-KLH** Attenuation in drug self-administration and a positive correlation between plasma drug concentration and antibody titer in rats.[77] Mitigation in drug-induced physiologic effects and lowered brain drug concentration in rats.[78] **SMA-TT** Decreased drug levels in vaccinated mice and attenuation in drug acquisition and reinstatement.[84]
Cathinone		**α-PVP-KLH, MDPV-KLH** Decreased locomotor activity and self-administration behavior in rats.[85] Decreased reinforcing effects of drug in high doses of vaccine. However, failure in Altering self-administration behavior in rats.[86]
Synthetic cannabinoids		**Drug targeting haptens** Cross reactivity for two different class of synthetic cannabinoids, decrease in locomotion and temperature in rats.[94]
Ketamine	**NK-N-COOH, KET-N-COOH, HNK-N-COOH** Antibody response against ketamine and 6-Hydroxynorketamine.[97]	

oxycodone and heroin. In terms of animal studies, a vaccine was developed by conjugation of an oxycodone hapten to tetanus toxoid (Oxy-TT) which was shown to be effective in several studies. A recent study showed a 50% lower oxycodone brain concentration in Oxy-TT rats compared to TT rats 30 minutes after injection and a significant decrease in self-administration under progressive ratio conditions (increased workload) in vaccinated rats.[22] Due to the lack of pre-vaccination screening methods for predicting vaccine clinical efficacy against drugs of abuse, biomarkers have been investigated extensively. Regarding the development of an effective oxycodone vaccine, a higher affinity of hapten-specific naïve B cells for oxycodone was shown to be associated with greater efficacy of vaccination in blocking oxycodone in mice's brain.[23]

Heroin: A unique challenge regarding heroin is its rapid metabolism to 6-acetylmorphine (6-AM) and further metabolization to morphine.[24] To address this, researchers have designed a "dynamic" vaccine that targets heroin and its metabolites.[25] Rats were vaccinated with the carrier protein keyhole limpet hemocyanin (KLH) alone or linked with either heroin haptens (Her–KLH) or morphine haptens (Mor–KLH), and the results were significant for an effective blockade of heroin activity and prevention of the drug abuse in vaccinated rats.[25] The idea of a dynamic vaccine that creates different antibodies against a substance with a rapid metabolism by presenting multiple haptenic epitopes to the immune system can be promising and deserves more research.[25] In another study investigating reduced behavioral effects of heroin as a result of vaccination with morphine conjugate vaccines, M(Gly)4-KLH vaccine was investigated. It has been demonstrated that vaccination with M (Gly)4-KLH was associated with high concentration of antibodies with strong affinity for heroin, 6-AM and morphine, maintained high serum levels of all three opioids as a result of retention and lower heroin-induced locomotor activity.[26] This study signifies the importance of targeting opioid metabolites in development of a potential vaccine.

Another interesting vaccine is a dual vaccine for the treatment of heroin use disorder and prevention of HIV-1 infection among IV drug users. This vaccine includes a synthetic heroin analog (MorHap) and a 42 amino acid V2 loop peptide from the A/E strain of HIV-1 gp120 envelope protein with liposomes containing monophosphoryl lipid A as an adjuvant. The results were significant for high endpoint titers for HIV and MorHap and attenuation in heroin-induced antinociception and hyper locomotion.[27] Dual targeting HIV-1 and heroin addiction with the same vaccine can be beneficial in preventing HIV-1 infection in heroin users.[27]

Morphine: KLH-6-SM is a conjugate vaccine comprised 6-succinylmorphine linked to lysine groups on KLH.[28] A preclinical study showed an increase in antibody levels, attenuation in behavioral responses to morphine, and a 25% percent reduction in brain levels of morphine in rats.[28] This vaccine's potential ability to produce the anti-morphine antibodies in a sustained manner and decrease the behavioral effects of morphine deserves more research due to its potential therapeutic benefits.[28]

Fentanyl: Fentanyl is a synthetic opioid with 50–100 times greater potency than morphine.[29] Additionally, the longer half-life of fentanyl requires multiple or higher doses of naloxone to be administered in order to reverse overdoses.[30] There are several preclinical animal studies for a fentanyl vaccine. In a recent study on mice, the vaccinated group with the FEN-CRM vaccine with adjuvants dmLT or LTA1 showed blockade of drug-related analgesia and decreased CNS penetration of drug.[31] In another study, a fentanyl-tetanus toxoid (TT) conjugate vaccine produced an up to 33-fold antinociceptive potency shift and significant protection from lethal fentanyl doses in mice.[32] A different study analyzed the effectiveness of the fentanyl-TT vaccine by using a fentanyl vs food choice procedure in rats. The result was an approximate 22-fold potency shift in fentanyl vs food choice, which was as effective as the approved treatment naltrexone, and a significantly blunted fentanyl reinforcement in rats.[33] Another study looked at the effectiveness and selectivity of a fentanyl-TT conjugate vaccine in altering the behavioral and pharmacokinetics of fentanyl in rhesus monkeys. It showed significant potency shifts in fentanyl behavioral effects with a substantial change of fentanyl potency to produce antinociception more than tenfold, which was similar to the effect of naltrexone.[34] Unfortunately, continuing development of synthetic fentanyl analogs with different chemical structures challenges the efficacy of any vaccine.[35] However, using the vaccine as an adjunct to standard therapy and as a harm reduction approach deserves more research.

Nicotine

Cigarette smoking is the leading preventable cause of disease and mortality in the US. An estimated 30.8 million adults in the United States currently smoke cigarettes[36] and more than 16 million Americans live with a smoking-related disease.[37] According to the World Health Organization, five million people die from tobacco-related diseases annually, and an estimated 8 million will die by 2030 if the current trends continue.[38]

Nicotine binds to acetylcholine receptors in the brain, releasing several neurotransmitters, most notably dopamine. It causes dependence by the α4β2 subtype of the nicotinic acetylcholine receptor, stimulates the mesolimbic reward system where dopamine is secreted, and inhibits monoamine oxidase B, which is essential for the catabolism of dopamine, leading to higher average dopamine concentrations in smokers compared to non-smokers.[39]

Currently, FDA-approved smoking cessation medications include nicotine replacement therapy (patch, spray, gum, lozenge, and inhaler), varenicline, and bupropion.[40] Although there is no effective vaccine in clinical use today, nicotine

vaccines have been studied extensively in recent decades. Due to the less physiologically-active nature of nicotine metabolites compared to its parent compound, nicotine, drug vaccine production aims to resemble nicotine.[7]

NicVax: This is the only nicotine vaccine that has progressed to a phase 3 clinical trial. It uses *Pseudomonasaeruginosa* exoprotein A as a carrier. Unfortunately, the entire data is not available for analysis.[41] A phase 3 study of 558 smokers investigated the effectiveness of NicVAX in preventing relapse when combined with varenicline treatment and behavioral support. It showed that the vaccine was ineffective in increasing abstinence from smoking when combined with standard therapy.[42] However, abstinence rates in the top 50% antibody responders were significantly higher compared to placebo which was hypothesized that could be related to a larger sample size of 50% subgroup compared to other subgroups.[42] Although there were no differences in severe adverse events, more adverse events related to NicVax were reported.[42] In another study using the single-photon emission computed tomography (SPECT) to evaluate the effect of NicVax on the amount of nicotine that binds to b2*-nAChRs in the brain, there was a 12.5% reduction in nicotine binding in the vaccine group which clinically manifested as a 50% reduction in cigarette use and significantly fewer cravings for cigarettes.[43]

TA-NIC: This is a conjugate vaccine that was first developed in 1997 using a nicotine hapten conjugated to recombinant cholera toxin b as a carrier protein.[44] A Phase 1 clinical trial showed substantially higher quit rates among those receiving TA-NIC compared to placebo. In the study, 8% in the placebo group reported abstaining at their last visit or at 12 months compared to 38% among groups that received the vaccine.[45] However, there was a Phase 2 clinical trial conducted in 2009 in which the results have never been published.[46]

Nic-Qb (NIC002): Is a conjugate vaccine that uses a virus-like particle formed by the coat protein of the bacteriophage Qb as a carrier.[47] In animal studies, this vaccine is associated with higher levels of nicotine-specific IgG titers and reduced nicotine levels in the brain of mice compared to the control group.[48] Results of a phase 1 clinical trial have shown antibody response in 100% of the subjects, with the development of nicotine-specific IgM antibodies at day seven and nicotine-specific IgG antibodies at day 14, without any serious adverse events. To increase antibody levels, a second dose, or the addition of alum was performed.[48] Additionally, a phase 2b trial with 341 smokers assessed self-reported abstinence from smoking confirmed by a carbon monoxide concentration in expired air, antibody response, and cravings via a questionnaire.[39] The vaccine was considered safe, and the abstinence rate was higher in the second month (Nicotine-Qb (47.2%) vs placebo (35.1%) ($P = 0.036$)). There was a 20.2% difference in the continuous abstinence rate after 12 months between placebo group and high antibody response group; however, only one-third of the subjects achieved sufficient antibody levels.[47]

SEL-068: This is a synthetic nano-vaccine that has been reported to have dose-dependent inducing effects on anti-nicotine antibodies in pre-clinical studies.[49] In order to determine the safety and pharmacodynamics of SEL-068, a phase 1 clinical trial with 82 participants was conducted. Although the trial was completed in 2013, no results have been published.[50]

Niccine: This is a conjugate vaccine with tetanus toxoid as a carrier.[51] A Phase 2 clinical trial showed a non-relapse rate at one year of 43.3% for the Niccine plus varenicline group versus 51.1% for placebo. Although nicotine antibody levels increased in the intervention group, the relapse rate has been found to be unrelated to the vaccine.[51]

NIC7-001, NIC7-003: This is a conjugate vaccine comprised a conjugate of 5-aminoethoxy-nicotine (Hapten 7) and a mutant diphtheria toxin (CRM197) as the carrier.[52] A pre-clinical study showed the generation of anti-nicotine antibodies in primates with the potential to decrease the drug's concentration in the brain.[52] Another phase 1 clinical trial was completed in 2015. However, the results have never been published.[53]

Regarding the investigation of anti-drug monoclonal antibodies (mAbs) for the development of a successful immunotherapeutic strategy for nicotine, in a pre-clinical animal study investigating Nic311 (a nicotine-specific monoclonal antibody), results were significant for lower brain levels of nicotine and reduced locomotor activity in rats that were vaccinated with a combination of active immunization and Nic311. However, neither was as effective as the combination of two when administered alone.[54] This study signifies the importance of combination therapy in a possible future vaccine design.

Cocaine

Cocaine is a stimulant with strong addictive potential via blockade of the reuptake of multiple monoamine neurotransmitters, most importantly dopamine.[55] In the US in 2020 among people 12 years or older, 1.9% (or about 5.2 million people) reported

using cocaine in the past 12 months.[56] Additionally, in 2020, approximately 19,447 people died from an overdose involving cocaine.[56]

Currently, there is no FDA-approved pharmacotherapy for cocaine use disorder. Although vaccine studies have shown promise in treating cocaine use disorder, the current literature does not strongly indicate any clinically effective vaccines. Two vaccines investigated extensively for cocaine use disorder are TA-CD and dAd5GNE.

TA-CD: This is a conjugate vaccine that uses succinyl norcocaine as a hapten and rCTB as a carrier. TA-CD has been designed to induce the formation of anti-cocaine antibodies.[57] This vaccine covalently links succinylnorcocaine (SNC) to cholera toxin B (rCTB).[58,59] A phase 2a trial showed a relationship between attaining high (≥43 μg/mL) IgG anti-cocaine antibody levels and reduced cocaine use, but only 38% of the vaccinated subjects attained these IgG levels, and they had only two months of adequate cocaine blockade.[57] A phase 3 trial with 300 subjects has been conducted, and although after week 8 statistically more vaccinated than placebo subjects attained abstinence for at least two weeks of the trial (24% vs 18%), and the high IgG group had the most cocaine-free urines for the last two weeks of treatment (OR = 3.02), neither were clinically significant. Additionally, compared to the earlier phase IIb trial, even though a higher percentage of subjects reached high levels of antibodies, the vaccine did not show a significant decrease in outpatient cocaine use.[60]

dAd5GNE: This is comprised of the cocaine analog GNE conjugated to the proteins of a disrupted adenovirus type 5 produced with a combination of lecithin and carbomer homopolymer.[61] In a study on nonhuman primates, the vaccine was associated with reduced cocaine occupancy in the brain, evidenced by positron emission tomography (PET) and the radiotracer [11C]PE21 measurement.[62] In another study, the vaccine effectively mitigated the effects of cocaine and its metabolites on different organs, including; the central nervous system, adrenal gland, spleen, lung, kidney, and liver in nonhuman primates.[63] With regard to human studies, a phase 1 clinical trial for assessing the safety and preliminary efficacy of the dAd5GNE vaccine with 30 participants is ongoing.[64]

In addition to conjugate vaccines, enzyme-based clinical trials were conducted regarding cocaine use disorder, including RBP-8000 and TV-1380.[65,66] Enzyme therapy has been recognized as a promising approach in cocaine overdose treatment.[67] TV-1380 is a fusion protein of mutated butyrylcholinesterase (BChE) with a more significant catalysis effect for cocaine.[68] In animal studies, TV-1380 has been shown to be effective in decreasing intoxicating effects and cocaine-seeking behavior.[69] In a phase 2 clinical trial with 208 participants to evaluate the ability of TV-1380 to facilitate abstinence in cocaine-dependent patients, compared to none in the placebo group, 6% of participants in TV-1380 groups reached abstinence, a non-significant difference. However, there was a dose-dependent increase in the percentage of urine samples testing negative for cocaine metabolites during weeks 5–12; 14.6% for the TV-1380 group, compared to 4.7% for the placebo group.[66] RBP-8000 is a thermostable double mutant form of CocE (cocaine esterase) with a half-life of 1 hour in animals.[70] In a preclinical animal study on primates, CocE intervention group had a three times faster elimination rates of cocaine from their brains.[67] Additionally, in a clinical trial with 29 cocaine using subjects, a decrease up to 90% in plasma cocaine concentrations and attenuation in physiological effects of cocaine was shown.[65]

Regarding the employment of biomarkers in the process of vaccine development and subject selection, based on a phase 2b clinical trial comparing cocaine-positive urines after vaccination in two groups of patients based on β-hydroxylase (DBH) gene level in brains of the subjects, cocaine-positive urines in subjects with the low DBH level genotype dropped from 77% to 51% on vaccine. However, subjects with normal DBH level genotype dropped from 83% to 72%.[71]

In terms of studies regarding usage of the drug specific monoclonal antibodies (mAbs), GNCgzk IgG was shown to be effective in the prevention of acute toxicity and lethality of cocaine in mice, which could be useful in treatment of overdoses in humans in the future.[72] In another study, vaccination of mice with AAVrh.10antiCoc.Mab, an AAVrh.10 gene transfer vector expressing anti-cocaine monoclonal antibody GNC92H2, resulted in sequestration of cocaine in the blood and reduced cocaine-induced behavioral effects.[73]

Methamphetamine

Based on National Survey on Drug Use and Health (NSDUH) data, among people 12 years or older in 2020, an estimated 0.6% (or about 1.5 million people) had a methamphetamine use disorder in the past 12 months.[74] Geographically, methamphetamine use was greater in the western US compared to eastern parts of the country. Less than 30% of adults

with methamphetamine use disorder received treatment in the past year.[74] High rates of co-occurring substance use and overlapping mental illness among methamphetamine users are particularly concerning.[75]

Methamphetamine and its compound amphetamine are in the class of substituted phenethylamines.[76] These strong psychostimulants modulate multiple neurotransmitters, including dopamine, norepinephrine, serotonin, GABA, and histamine, via inhibiting vesicular monoamine transporters and dysregulation of transmitters at nerve endings.[76,77]

Currently, there is no pharmacologic treatment for methamphetamine use disorder. Available therapies revolve around different psychotherapy methods and relapse prevention programs. Clinical studies indicate that contingency management, CBT, behavioral activation, and exercise might help maintain abstinence.[78] For the development of anti-METH vaccines, different carriers, including tetanus toxoid (T.T.), diphtheria toxoid (D.T.), bovine serum albumin (BSA), and keyhole limpet hemocyanin (KLH), have been investigated extensively.[79] In animal studies, both passive and active vaccines have shown promising results.[80,81]

In one of the first-generation anti-meth vaccines, rats were vaccinated with MH6-KLH (a vaccine containing meth hapten MH6 conjugated to KLH), which resulted in an attenuated percentage reaching the IV self-administration threshold (66% vs 33%), and showed a positive correlation between plasma meth concentration and antibody titer.[82] In another study investigating MH6-KLH, the vaccine was shown to be effective in mitigating drug-induced effects in thermoregulation and hyperlocomotion and lowering brain meth concentrations.[83] Another preclinical study with a vaccine consisting of a hapten (succinyl-methamphetamine, SMA) attached to tetanus toxoid (SMA-TT) using aluminum hydroxide as the primary adjuvant was effective in attenuating acquisition and reinstatement of meth place conditioning. Moreover, the brain levels of methamphetamine significantly decreased in vaccinated mice compared to the control group.[84]

Besides animal studies, there are several clinical trials for methamphetamine vaccine development. In a preclinical study, anti-METH mAb7F9 (ch-mAb7F9(IXT-m200)) was found to decrease addiction-related behavior in rats.[85] A double-blind placebo-controlled phase 1 clinical trial with 42 participants was conducted to determine the safety and tolerability of single, ascending intravenous doses of ch-mAb7F9 in healthy subjects via physical examinations and adverse events, vital signs, electrocardiogram (ECG), and clinical laboratory testing. However, results have never been published.[86] Another phase 1/2 clinical trial with 56 participants to determine the effects, safety, and tolerability of IXT-m200 on the pharmacokinetics of methamphetamine in subjects with methamphetamine use disorder has been completed but not yet published.[87]

Cathinone

Cathinones, also commonly known as “bath salts”, are psychostimulant drugs that, except for the presence of an aryl ketone, share a similar chemical structure with amphetamines.[88] Cathinone acts via inhibition or reversal of the monoamine reuptake transporters.[89] Two highly reinforcing synthetic cathinones are α-pyrrolidinopentiophenone (α-PVP) and 3.4-methylenedioxypyrovalerone (MDPV).[90] Although at the current time no ongoing clinical trials exist, several preclinical studies on animals have been conducted. Vaccines against α-PVP and MDPV were developed using hapten immunoconjugates α-PVP-KLH and MDPV-KLH mixed with CpG oligodeoxynucleotide (CpG ODN) and alhydrogel alum. Results of a pre-clinical trial were significant for decreased locomotor activity and self-administration behavior in rats.[90] In another preclinical study investigating active vaccination to reduce the reinforcing effects of MDPV, rats were trained to self-administer cocaine due to its similarity to MDPV. Results were significant for a decrease in potency of MDPV’s reinforcing effects in high doses of vaccine. However, the vaccine could not alter the acquisition of cocaine self-administration behavior.[91]

Synthetic Cannabinoid

These synthetically manufactured substances exert their effects mainly by mimicking the effects of a substance found in cannabis called tetrahydrocannabinol (THC) which causes activation in CB1 receptors in brain.[92] Currently, treatment options for synthetic cannabinoids are limited to symptomatic treatment.[93] Although there are no clinical trials undergoing now, in a study to determine the optimal vaccine composition, three haptens were identified to be successful in creating cross-reactivity for two different drug classes of synthetic cannabinoids. Furthermore, it has been demonstrated

that a vaccine cocktail comprising two haptens could be effective in targeting over 10 different synthetic cannabinoids, and sequestration of the drug even when administered by vaping or intraperitoneal injection.[94]

Ketamine

Ketamine is an anesthetic agent with non-competitive antagonist effects on N-methyl-D-aspartate (NMDA) receptors. Reinforcing effects and self-administration induction of the ketamine have been demonstrated in rats.[95] Due to its high abuse potential and growing popularity, ketamine was listed under new psychoactive substances (NPS).[4] Although the potential use of lamotrigine due to its effects on glutamate release inhibition and possible decrease in cravings was proposed, currently there are no approved pharmacotherapies for the treatment of ketamine use disorder.[96]

In terms of immunotherapeutic approaches to ketamine use disorder, three haptens including, norketamine-N-COOH (NK-N-COOH), ketamine-N-COOH (KET-N-COOH) and 6-hydroxynorketamine-N-COOH (HNK-N-COOH) were synthesized to target either ketamine or 6-hydroxynorketamine.[97] In pre-clinical animal studies, all three haptens induced immune response. Additionally, KET-N-COOH and 6-HNK-N-COOH haptens produced antibodies with up to 10-fold improvements in affinity for ketamine and/or 6-hydroxynorketamine, as compared to NK-N-COOH.[97] Immunotherapeutic approaches could be beneficial in treatment of intoxication or overdose of ketamine in the future.

Conclusion

While significant progress has been made in immunotherapeutic approaches for SUD, there is a long way to go. Despite the fact that there have been numerous pre-clinical studies with successful outcomes, no human trials have met a desired clinical endpoint. There are only two ongoing clinical trials, the dAd5GNE vaccine for cocaine, with an estimated completion date of December 2025,[64] and Oxy(Gly)4-sKLH vaccine for oxycodone with an estimated completion date of December 30, 2023.[21] Potentially, the unstable nature of most drugs, polysubstance use, need for multiple doses of vaccine, adjuvant selection processes, and consistent production of new synthetic drugs with structural dissimilarity leads to suboptimal antibody responses for vaccines. With further development of efficacy improvement strategies, novel vaccine designs, discovery of biomarkers to better predict vaccine responses and potential subject selection, and a more in-depth understanding of the behavioral effects of vaccines, groundbreaking changes in SUD's treatment and prevention are anticipated in a foreseeable future.

Abbreviations

SUD, substance use disorder; mAB, monoclonal antibodies; BSA, bovine serum albumin; PAMPs, pathogen-associated molecular patterns; PRRs, pattern recognition receptors; TLR, Toll-like receptors; MPA, Monophosphoryl lipid A; ELISA, enzyme-linked immunosorbent assay; RIA, radioimmunoassay; LCMS, liquid chromatography with mass spectrometry; OUD, opioid use disorder; KLH, keyhole limpet hemocyanin; SPECT, single-photon emission computed tomography; PET, single-photon emission computed tomography, NSDUH, National Survey on Drug Use and Health; THC, tetrahydrocannabinol; NMDA, N-methyl-D-aspartate; NPS, psychoactive substances.

Disclosure

The authors report no conflicts of interest in this work.

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