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Immunotherapeutic Strategies for Treating Opioid Use Disorder and Overdose

Rachel Luba[1,*], **Suky Martinez**[1], **Jermaine Jones**[1], **Marco Pravetoni**[2], **Sandra D Comer**[1]

[1]New York State Psychiatric Institute/Columbia University Irving Medical Center Division on Substance Use Disorders

[2]University of Washington, School of Medicine, Department of Psychiatry and Behavioral Sciences, Department of Pharmacology, Center for Medication Development for Substance Use Disorders and Overdose, Seattle, WA

Abstract

Introduction: Development and implementation of effective treatments for opioid use disorder (OUD) and prevention of overdose are urgent public health needs. Though existing medications for OUD (MOUD) are effective, barriers to initiation and retention in treatment persist. Therefore, development of novel treatments, especially those that may complement existing treatments, is needed.

Areas covered: This review provides an overview of vaccines for substance use disorders (SUD) and mechanisms underlying their function and efficacy. Next, we focus on existing preclinical and clinical trials of SUD Vaccines. We focus briefly on related strategies before providing an expert opinion on prior, current, and future work on vaccines for OUD. We included published findings from preclinical and clinical trials found on Pubmed and ScienceDirect as well as ongoing or initiated trials listed on ClinicalTrials.gov.

Expert opinion: The present opioid overdose and OUD crises necessitate urgent development and implementation of effective treatments, especially those that offer protection from overdose and can serve as adjuvants to existing medications. Promising preclinical trial results paired with careful efforts to develop vaccines that account for prior SUD vaccine shortcomings offer hope for

[*]Corresponding author: Rachel Luba; Rachel.Luba@nyspi.columbia.edu; 1051 Riverside Drive Rm 3737 New York, NY 10032.

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current and future clinical trials of opioid vaccines. Clinical advantages of opioid vaccines appear to outnumber disadvantages which may result in improved treatment options.

Keywords

Vaccines; Immunotherapies; Opioid Use Disorder; Substance Use Disorders; Heroin; Oxycodone; Fentanyl; Opioids; Nicotine; Cocaine

1.0 Introduction

Approximately 1.6 million Americans displayed symptoms consistent with Opioid Use Disorder [OUD] in 2019 [1]. In the United States, OUD is a major contributor to premature death, with 80,590 opioid-overdose related deaths in 2021, the highest number ever recorded [2]. During the COVID-19 pandemic, the incidence of overdoses increased substantially [3–5]. Though its origins are complex and multi-faceted, the current opioid epidemic presents a public health crisis, and efforts to understand and effectively treat OUD are critical [6–7].

Currently, several medications are approved by the U.S. Food and Drug Administration [FDA] to treat OUD, including methadone, buprenorphine, naltrexone, naloxone, and their combination [e.g., Suboxone] or extended-release formulations [e.g., Vivitrol]. Though the effectiveness of these medications has strong empirical support, barriers to implementation and high relapse rates among those who do start treatment contribute to increased risk for opioid overdose [8–10]. Further complicating efforts to treat those with OUD is the recent proliferation of high-potency synthetic opioids [HPSO; fentanyl, carfentanil, and related analogs and, more recently, benzimidazole opioids known as “nitazenes”] into opioid and other drug supplies [7]. HPSO are opioid analogues estimated to be more potent than heroin and therefore markedly increase the risk of opioid-related overdose given their rapid onset of action and narrow “therapeutic window” [the dose that produces analgesic response compared to the dose that produces respiratory depression [11–13]. The presence of HPSO in illicit opioid supplies appears to be complicating effective use of MOUD [2, 14–16]. Further, the presence of HPSO in opioid and other drug supplies appears likely to persist given high profit margins for drug producers and ease of distribution [17–18].

Together, these factors necessitate urgent exploration of novel interventions to treat OUD. One such approach, opioid vaccines, will be explored in this review. First, we will provide a brief overview on the mechanisms underlying vaccines for treating substance use disorders [SUD] more broadly. Next, this review will provide a brief overview of existing preclinical and clinical work on vaccines for nicotine, cocaine, and methamphetamine, with an emphasis on limitations of prior work, followed by a summary of preclinical and clinical work with vaccines for OUD. Finally, we will review literature on factors influencing response to vaccines for SUD, related work with monoclonal antibodies [mAb], and future directions. Finally, this review will provide an expert opinion on the current status of opioid vaccines and related interventions and outline future directions. We searched Pubmed and ScienceDirect databases between August 3rd, 2022 and October 30th, 2022 and included published findings from preclinical and clinical trials as well as ongoing or initiated trials listed on ClinicalTrials.gov. Keywords used for this search

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included “vaccines for SUD”, “vaccines for cocaine”, “vaccines for nicotine”, “vaccines for methamphetamines”, “vaccines for opioids”, “immunotherapies for SUD”, “monoclonal antibodies” and “biologics for SUD”. One-hundred-and-twenty-five sources are included in this review.

2.0 Vaccines for SUD: mechanisms of action and definitions

The goal of vaccines for treating SUD is to elicit production of antibodies that bind to the target drug molecules in serum. This binding of drug molecules to antibodies creates a drug: antibody complex that is too large to pass through the blood-brain barrier [BBB; Figure 1; 19–21]. In preventing transfer across the BBB, vaccines decrease the amount of unbound [free] drug circulating in and activating receptors in the brain, thus reducing any neurobiological or behavioral changes that typically occur with drug administration [19, 21]. In addition, vaccine-induced antibodies have been shown to reduce free drug circulation in organs such as lungs or heart which may further contribute to the protective effects of vaccines against respiratory depression and bradycardia [22]. Generally, vaccines for SUD are composed of several components that are intramuscularly or subcutaneously injected [see Figure 2]. Drug-derived haptens are small molecules that do not produce an immune response on their own but are designed to model the chemical structure of the target drug. Typically, a carrier protein or immunogenic carrier of viral, bacterial, or other foreign origin is attached to the hapten to elicit an immune response. Finally, the conjugate immunogens consisting of the hapten and carrier protein combination are paired with an adjuvant, which further enhances the strength and durability of the immune response [Figure 2]. Currently, there are 6 existing adjuvants that have been developed and approved in licensed vaccines for human use [23], and many others are at different stages of clinical development. After vaccination, usually with several doses delivered over time, generation of drug-specific polyclonal antibodies is triggered.

Generally, immune response to vaccines is mediated by a variety of interconnected cellular and molecular processes. B cell lymphocytes, which are white blood cells that produce antibodies, work with T cells to recognize and mount an immune response to antigens [21, 24]. Several types of T cells play a role in the immune response against different categories of antigens. Generally, specialized subsets of helper T cells [Th] work with B cells in producing a humoral response involving production of antibodies against the target. Vaccines for SUD are conjugate immunogens that stimulate both hapten-specific B cells and carrier-specific T cells. Hence these vaccines rely on CD4 + T cell-dependent activation of B cells, which occurs when either B cells bind the hapten on the hapten-carrier conjugate, or antigen-presenting cells such as macrophages or dendritic cells present the antigen on their surface via a major histocompatibility [MHC] process. Once this occurs, T cells recognize the carrier-derived T cell epitopes, bind to the MHC with support from CD4+ co-receptors, and activate B cell response. Once activated, B cells produce drug-specific antibodies that bind and neutralize their pharmacological effects. Use of carrier proteins appears to recruit carrier-specific CD4+ T cells to trigger the necessary CD4+ T cell-dependent B cell activation required to produce antibody responses [19, 25–26]. The immune response to vaccines is generally measured by analysis of blood samples for the presence of drug-specific antibodies. Recent advances have allowed for more comprehensive

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analyses including measurement of drug-specific B cell lymphocytes and carrier-specific T cells and characterization of antigen-presenting cells [APC] such as dendritic cells or macrophages. Efforts to characterize hapten-specific B cells and carrier-specific T cells and their relation to anti-drug antibody production in SUD vaccines may help to elucidate individual differences in vaccine response [21].

One of the clinical shortcomings that can be associated with use of therapeutic vaccines is variability in individual response to active immunization. Variability appears to stem from several factors, including specific vaccine components, vaccine dose and schedule of vaccination, individual and/or baseline differences in immune response, sex, age, genotype, and individual drug use patterns [20–21, 27–28]. These factors, along with drug-specific [e.g., stoichiometry of target drug versus antibody binding site mole ratios] factors must be considered in developing effective vaccines for SUD. Another important consideration is cross-reactivity, or an observable immune response to pathogens/molecules not specifically targeted by the vaccine.

2.1 Nicotine vaccines

To date, a number of nicotine vaccines have been tested in preclinical and clinical models and vary based on choice of carrier [virus linked particles [VLP], bacterial toxin components] and nicotine derivatives [29]. Vaccines targeting nicotine stimulate production of antibodies that bind to nicotine and reduce or block its ability to cross the BBB. As highlighted above, the strength of a nicotine vaccine's efficacy is generally measured by the concentration of nicotine-specific IgG antibodies or antibody titers produced post-vaccination [30]. More recent evidence indicates that other factors affecting vaccine efficacy may be related to the IgG subclasses [e.g., IgG1-3] and affinity for the target compound [22, 31–32].

2.1.1 Preclinical studies of nicotine vaccines—Preclinical studies examining nicotine vaccines suggest promising effects, including greater serum nicotine concentrations in vaccinated versus unvaccinated rodents, evidence of sequestration of nicotine by antibodies, and lower concentrations of nicotine in the brain of vaccinated rodents [30, 33–37]. Over time, repeated nicotine dosing appears to attenuate the results of vaccination in animals, but even with repeated dosing nicotine reaches the brain more slowly and therefore produces less reinforcing effects in vaccinated animals [30, 38]. With regard to acquisition and maintenance of nicotine self-administration, animal models have shown vaccines can block or significantly attenuate these behaviors [30, 39]. Broadly, findings from preclinical studies of nicotine vaccines have been replicated across laboratories and across specific vaccine compounds, bolstering the strength of findings [30]. One important caveat is that most animal models of vaccines involve intravenous or subcutaneous injection of nicotine by itself, which clearly differs from inhalation of nicotine, tobacco, and the numerous other chemicals present in cigarettes smoked by humans [30]. Yet, vaccines against nicotine have shown pre-clinical efficacy in rats exposed to cigarette smoke in inhalation models [36]. Preclinical studies have largely utilized Fruend's adjuvant, which though typically linked to a strong immune response, has an unfavorable safety profile in humans, limiting use in clinical trials [35]. Despite promising efficacy in various pre-clinical models, nicotine

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vaccines have shown a relatively low threshold of efficacy against nicotine doses equivalent to more than 2 cigarettes [40].

2.1.2 Clinical studies of nicotine vaccines—In spite of promising preclinical findings, clinical trials of nicotine vaccines have been less successful, and have generally not replicated preclinical findings. To date, five nicotine vaccines have been tested across 16 Phase I-III clinical trials [see 21, 29, 41 for overview]. A proof-of-concept study on one candidate vaccine [TA-Nic [NCT00633321; 42]] was initiated between 2006 and 2007, but no peer-reviewed findings were ever published and development was halted. A Phase II trial of Niccine, a nicotine-hapten conjugate vaccine, utilized a relapse-prevention model, and failed to find significant effects of vaccination on rates of relapse, smoking status, time to relapse, or abstinence across 1 year. Though anti-nicotine antibody levels increased in the vaccinated group, antibody level was not associated with relapse rate, and further development of Niccine was halted [43]. A third candidate vaccine, Nic-002, was evaluated across three clinical trials. An initial trial evaluated the safety and tolerability of Nic-002 in 40 nonsmoking volunteers and demonstrated a favorable safety profile with a high antibody response [35]. A larger Phase II study in 341 adult smokers suggested similar rates of abstinence between active vaccine and placebo groups, though antibody titer level at month 2 appeared to be an important moderator, such that those deemed to have a high antibody response demonstrated significantly higher rates of abstinence between 2 and 6 months post-vaccination and at 12 months post-vaccination [44]. As inflammatory, influenza-like symptoms were reported among those receiving Nic-002, efforts were made to reformulate the vaccine for a subsequent Phase IIb trial. However, results from this trial were not published or reported, and further development appears to have been halted [41].

NicVAX is the most thoroughly tested candidate vaccine in human trials [see 45–47]. Initial studies assessed dosage and vaccination schedule and suggested NicVAX was well tolerated with an acceptable safety and side-effect profile. A subsequent Phase IIb trial [46] suggested that antibody response was reliably and significantly associated with smoking cessation and long-term abstinence rates, with those demonstrating the highest antibody response demonstrating the most robust effects. However, two subsequent Phase III trials of NicVAX failed to replicate these findings. Though NicVAX appeared safe and well-tolerated across Phase I and II trials, Phase III trials demonstrated identical rates of abstinence between active and placebo vaccine conditions [11%; 48]. A nicotine vaccine consisting of nicotine-CRM197 adjuvanted in alum/CpG was tested by Pfizer [48–49], but results are not available. One final vaccine candidate, SEL-068, was tested in a clinical trial that recruited 82 participants in Belgium between 2011 and 2013 but no results have been made publicly available to date and development appears to have been halted [NCT01478893; 51].

Together, promising preclinical findings have failed to replicate in the vast majority of clinical trials of nicotine vaccines [21, 29–30] and one 2012 Cochrane review thus concluded that no current evidence supports nicotine vaccine-related enhancement of long-term smoking cessation rates [48]. Prior work suggests that human trials of nicotine vaccines have failed to replicate preclinical findings due to insufficient anti-nicotine antibody production, insufficient specificity or affinity of antibodies produced from vaccination, or weaknesses in study design that may have contributed to low motivation to quit [41].

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Further, across preclinical and clinical trials of nicotine vaccines, high individual variability in antibody titer concentration post-vaccination, both a facet of general variability of immune response and variability in tested products, makes development of an effective vaccine quite challenging. Future work must identify factors driving individual variability in immune response in order to develop vaccines that result in fewer non-responders, either by increasing mean antibody response or reducing variability [30].

2.2 Cocaine vaccines

To date, several preclinical and clinical trials have been conducted to develop and test a therapeutic vaccine for cocaine. Unlike with nicotine vaccines, just two candidate vaccines have progressed to human trials, with published data only available for one.

2.2.1 Preclinical studies of cocaine vaccines—Preclinical trials of cocaine vaccines began in the early 1990's. Between 1992 and 2005, several groups of researchers developed and tested several vaccine iterations utilizing different haptens, carrier proteins, and adjuvants across species [52]. Early work by Janda and colleagues developed and tested two haptens [GNC and GND] in rat models. This work demonstrated suppression of cocaine-induced locomotor activity and lower levels of cocaine in the brains of vaccinated rats compared to controls [53–54] and prevention of cocaine reinstatement in vaccinated rats [55]. Controls in these studies included animals injected with monoclonal antibodies, somewhat distinguishing results from prior studies utilizing placebo-vaccines as controls.

Subsequent preclinical work by Fox and colleagues testing a distinct conjugate [TA-CD] vaccine that was later adapted for human trials, demonstrated lower cocaine levels in the brains of vaccinated mice [56] and high enough antibody response to diminish cocaine self-administration in rats [57–58]. Exploration of a different cocaine vaccine in rhesus monkeys suggested a robust antibody response to vaccination [59]. Further work replicated prior findings that vaccination reduced cocaine levels in the serum, brain, and olfactory bulbs of vaccinated mice compared to controls [60]. A more recent examination of an additional cocaine vaccine [dAd5GNE] suggested similar findings with vaccination associated with reduced cocaine levels in the brains of vaccinated non-human primates [61–62] and reduced cocaine-induced hyperactivity among vaccinated animals [63].

2.2.2 Clinical trials of cocaine vaccines—To date, two cocaine vaccines have progressed from preclinical to clinical trials, with published data presently available only for TA-CD. The first clinical trial of TA-CD tested 3 vaccine doses in 24 participants vaccinated once per month for three months. TA-CD was well tolerated, anti-cocaine antibodies were detected following the second vaccination and higher mean antibody response in those receiving higher doses of TA-CD was observed [64–65]. Subsequent trials with TA-CD suggested that individuals demonstrating a higher antibody response post-vaccination appeared less likely to use cocaine or experience euphoric effects from cocaine during follow up [66]. Unfortunately, as with nicotine vaccines, high variability in antibody response was noted, and in one study 25–30% of participants demonstrated low antibody response [66]. In a subsequent larger trial only 38% of participants demonstrated a sufficient antibody response [767]. As observed in trials with nicotine vaccines, participants

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demonstrating a high antibody level appear to experience clinically meaningful results. For example, those with a high antibody response demonstrated fewer cocaine positive urine samples at follow up [67] and reported less reinforcing effects from smoked cocaine in a laboratory paradigm [68]. Still, this high variability made for difficult interpretation of findings and subsequent development of TA-CD was not pursued [20]. A Phase I clinical trial examining the safety and immunogenicity of dAd5GNE was initiated in 2015 but no results have been published to date, and the anticipated study completion date is December 2025 [NCT02455479; 69].

2.3 Methamphetamine vaccines

To date, a number of preclinical studies have examined the utility of methamphetamine vaccines and have demonstrated somewhat promising results. Broadly, this work has demonstrated that mice vaccinated against methamphetamines demonstrate a reliable and robust antibody response and appear to experience less reinforcing effects of methamphetamines [70]. Subsequent animal testing with a vaccine more viable in humans [using alum as an adjuvant] suggest reduced acquisition and reinstatement of methamphetamine self-administration in mice [71]. Additional conjugate vaccines have demonstrated reduced psychomotor effects, reduced self-administration of methamphetamines, and robust antibody response in vaccinated rats and mice [72–75]. Additional testing with alternative adjuvants has sought to bolster antibody response and demonstrated promising results [76–78]. Still, in spite of these promising initial findings no methamphetamine vaccines have progressed to human trials.

2.4 Opioid vaccines

Efforts to develop a vaccine targeting opioids dates back to the 1970's, with early work suggesting strong antibody response and high specificity from three vaccines targeting morphine derivatives in a rabbit model [79] and stimulation of antibodies associated with reduced heroin self-administration in non-human primates [80]. In spite of these early efforts, continued development of opioid vaccines declined with the advent of methadone as a treatment for OUD, and interest in vaccines for SUD did not return until the 1990's with a focus on cocaine vaccines [52]. Therefore, to date, few clinical trials have been carried out with opioid vaccines. There are some distinctions to note in the development of candidate vaccines for opioids in contrast to candidate vaccines for other drugs. Specifically, because opioids can have very different chemical structures [e.g., fentanyl vs morphine], and because many with OUD use a range of distinct opioids simultaneously and across time, a multivalent vaccine is considered necessary. Multivalent vaccines target a number of distinct target molecules simultaneously as they contain multiple individual hapten-carrier conjugates or multiple haptens conjugated to the same carrier. The advantages and disadvantages of this approach, paired with distinct clinical considerations associated with opioid vaccines will be discussed below.

2.4.1 Preclinical opioid vaccines—Though clinical trials exploring opioid vaccines are few, a wealth of recent preclinical data supports the utility and progression to clinical trials of vaccines targeting opioids. To date, several distinct candidate vaccines have been tested in animal models targeting heroin and its metabolites, hydrocodone, oxycodone,

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fentanyl, carfentanil, and other fentanyl analogs. Candidate vaccines have differed in terms of target opioid molecule and hapten. Early work using the KLH-6-SM vaccine [which consists of 6-succinylmorphine linked to lysine groups on KLH] reduced morphine-induced response and brain morphine levels in rats [81]. Given heroin's metabolism to three distinct compounds [6-mono-acetylmorphine [6-MAM], morphine, and morphine-6-glucuronide], some research groups have targeted candidate vaccines that take a multivalent approach, targeting multiple compounds at once. This multivalent approach has the capacity to address real-world drug use patterns as many with OUD use a variety of opioids either simultaneously based on what is available in the illicit drug supply, or due to alterations in drug use patterns over time [switching from prescription opioids to heroin for example; 20, 82]. Conjugate vaccines for opioids have broadly demonstrated robust antibody response to heroin and its metabolites, reduced opioid concentration in the brains of vaccinated animals, and reduced heroin-induced motor and behavioral activity, including declines in heroin-seeking behavior and self-administration [26, 83]. Some of this work suggests that cue- and stress-induced relapse appear less responsive to vaccination, though rats exposed to stress- and cue-induced self-administration paradigms after a period of abstinence appear to reinstate use in a less rapidly escalating manner compared to unvaccinated rats [84].

A conjugate vaccine targeting oxycodone demonstrated high specificity, protection against the respiratory effects of oxycodone, and low cross-reactivity to other opioids [85]. Fentanyl vaccines have also demonstrated promising effects in preclinical work, offering protection from overdose and attenuating the analgesic and respiratory effects of fentanyl in rhesus monkeys [86–87]. Sublingual and intranasal fentanyl vaccines have also been tested, with data suggesting reduced fentanyl levels in the brains of vaccinated mice [88].

Efforts to develop and test fentanyl and fentanyl-analog vaccines present unique challenges and further work is needed to determine whether a single vaccine can effectively target several molecules in the fentanyl chemical family or if multiple vaccines targeting each analog is necessary. One group demonstrated the efficacy of a fentanyl vaccine in reducing fentanyl-induced pharmacological and behavioral effects of fentanyl on its own [86] and heroin contaminated with fentanyl [89]. A second group of researchers showed reduced distribution of fentanyl, reduced fentanyl-induced analgesia, and reduced respiratory depression in vaccinated mice and rats [90]. Importantly, this vaccine did not appear to interfere with naloxone's ability to reverse respiratory depression [90]. More recent work to refine one fentanyl vaccine and test alternative adjuvants [LTA1 or dmLT] compared to alum suggests a more robust antibody response and more marked reductions in CNS distribution and fentanyl-induced analgesia with these adjuvants [88]. This study also supported intranasal vaccine administration [88]. Given evolution in drug supply over time, including increased synthesis of fentanyl analogs, a successful vaccine must demonstrate efficacy for fentanyl and related compounds, which may complicate development. To date, preclinical work with fentanyl vaccines suggests that they can effectively target fentanyl and carfentanil, eliciting high-affinity antibodies against both drugs in mice, and offering protection against opioid-induced respiratory depression [22,91]. Related work suggests preclinical efficacy against some fentanyl analogs [sufentanil, acetylfentanyl], but not others [alfentanil] suggesting that more work is needed to refine this approach [92]. In an ever-shifting landscape of HPSO, these compounds present somewhat of a moving target for

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vaccine developers, necessitating further work to develop and test vaccines that are highly targeted while also offering selective cross-reactivity to related HPSO compounds.

Efforts to increase efficacy of opioid vaccines have focused on manipulation of vaccine components in developing more effective, specific, and reliable candidates. Research conducted at Walter Reed Army Institute of Research on a heroin vaccine [Army Liposome Formulation [ALF]] found promising effects of ALF on analgesia and motor activity in vaccinated mice and rats [93–94]. Importantly, subsequent studies suggested increased efficacy of ALF with use of aluminum hydroxide as an adjuvant [95]. Similarly, researchers at Scripps Research Institute compared conjugation techniques and found greater efficacy with carbodiimide chemistry such that this technique produced greater reductions in heroin-induced antinociception in mice and heroin self-administration in non-human primates compared to a maleimide-based conjugate [96].

Work on a morphine-based hapten conjugated to KLH [M-KLH] has shed light on the potential development of multivalent opioid vaccines. On its own, M-KLH has demonstrated efficacy in reducing heroin, morphine, and 6-MAM distribution to the brains of vaccinated rodents, attenuating heroin-induced analgesia and respiratory depression, and reducing reinstatement of heroin self-administration [97–99]. Further work to deliver M-KLH simultaneously with an oxycodone vaccine suggests combined effects, such that co-administration of both vaccines reliably blocked 6-AM and oxycodone distribution [99].

Though somewhat less abundant, work testing oxycodone and hydrocodone vaccines largely replicates findings with heroin and morphine vaccines. Specifically, two separate research groups have developed and tested oxycodone- and hydrocodone-specific vaccines that generate antibodies specific to oxycodone and hydrocodone [100]. This research in rodents demonstrated vaccine-induced reductions in: distribution of target molecules to the brain [100–102], analgesia [100–102], self-administration [101–103], and respiratory depression [85, 101–102, 104]. Both groups developing and testing oxycodone and hydrocodone vaccines have also found that vaccine-generated antibodies do not bind to off-target opioids, do not interfere with naloxone in reversing overdose, and are not affected by maintenance on other off-target opioids or opioid antagonists [85, 101–102].

2.4.2 Clinical trials of opioid vaccines—One clinical study testing a morphine-based conjugate vaccine was conducted in Iran and supported the safety and tolerability of this vaccine. This trial examined a morphine-6-succinate hapten conjugated to bovine serum albumin [BSA] administered to 347 individuals with OUD. Though the authors report that the vaccine was well tolerated with minimal side effects, detailed reports on adverse events are not available. Similarly, no efficacy data from this trial have been made available for peer review, limiting interpretation of findings [105–106]. Currently, there is one ongoing clinical trial examining safety, tolerability, and preliminary efficacy of an oxycodone vaccine. This work, conducted by our group, is part of a multi-phase grant to explore an opioid vaccine targeting oxycodone [NCT04458545; 107]. Other opioid vaccines in development by our group will target heroin and fentanyl. Given promising preclinical findings, further clinical testing is a crucial next step in developing and refining opioid vaccines for clinical use.

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3.0 Other approaches [passive immunization]

Alternate efforts to elicit antibody response to target drug molecules have focused on passive immunization with monoclonal antibodies [mAb; see 21]. Passive immunization involves a similar mechanism as vaccination, but through direct delivery of high-affinity, anti-drug mAb. It has been proposed that this delivery system may reduce the individual variability seen with prior vaccinations and elicits a more rapid and reliable antibody response. Preclinical findings appear to support this hypothesis as shown in the use of anti-nicotine [108–109], anti-cocaine [56, 110–111], anti-methamphetamine [112], anti-opioid [113–115], and anti-phencyclidine [116] mAb. One clinical trial examining a mAb targeting methamphetamines showed an acceptable safety profile and mean half-life of mAb between 17 and 19 days [117]. A more recent clinical trial exploring a different anti-methamphetamine mAb [IXT-m200, NCT03336866; 118] was recently completed, though peer-reviewed findings are not yet available. Pre-clinical studies show that mAbs are effective in reversing the effects of fentanyl and carfentanil in mice and rats [119]. Findings that mAb may reverse opioid-related toxicity were somewhat unexpected, but if replicated, may provide rationale for further development of mAb as overdose-reversal agents. Additional preclinical and clinical studies of mAb are needed to further understand their efficacy and therapeutic utility.

Successful development of an opioid mAb may pose several advantages and disadvantages. As noted above, passive immunization with mAb may provide less variability in time course, including onset, duration, and offset of effects than vaccine-elicited antibody levels. Therefore, clinicians may have greater confidence in using an opioid mAb alone if the clinical effect is immediate, robust, and of known duration. As with vaccines, opioid mAb are expected to have low cross-reactivity to off-target opioids so they could be used in combination with another MOUD which provides greater flexibility for clinical use. Another potential advantage of an opioid mAb versus vaccine relates to the potential need for opioids to treat pain. The duration of antibody response with an anti-oxycodone vaccine is unclear both within and across patients, making it difficult to determine the exact course of action for someone who may recover from an OUD but later require treatment with an opioid [for example post-operatively]. An opioid mAb, however, may have a much shorter and more predictable duration of action within and between patients. One possible disadvantage of this approach is that mAb development is quite expensive. Additionally, currently mAb must be intravenously infused in a large volume for immediate effect, limiting utility in emergency [overdose-response] settings. Still, this approach appears promising and future efforts to develop and refine the use of mAb, especially in cost-effective ways, appears warranted.

4.0 Conclusion

Current rates of OUD and opioid-related overdose necessitate critical development and implementation of novel, effective treatments. Though prior clinical trials with vaccines for SUD have been somewhat disappointing, there is reason to believe that current efforts to develop and test vaccines for OUD can accomplish what previous vaccine candidates have not. Arming clinicians and patients with multi-faceted, cost-effective, and easy-to-deliver

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treatment options is of the utmost importance and adding an opioid vaccine to current MOUD options could improve therapeutic outcomes.

5.0 Expert opinion

Though stagnant for many years, development of opioid vaccines appears to be accelerating, and researchers may be in a unique position to develop and test candidate vaccines that account for prior shortcomings of other SUD vaccines. For example, numerous preclinical studies of opioid vaccines have sought to refine and test a number of adjuvants, haptens, and carrier proteins [21, 26]. These efforts may help to ensure that subsequent clinical trials are utilizing the most promising candidates. Further, efforts to learn from prior work, and account for and more effectively measure individual differences in vaccine response [and potential drivers of this variability] can aid in more effective vaccine development. Efforts to better understand and account for B-cell and T-cell activity, for example, can help to more accurately identify those most likely to demonstrate a good response to candidate vaccines [21, 32, 120]. In our current oxycodone vaccine trial, years of preclinical work to understand B and T cells, Fc effector functions, microbiome factors, and cytokine levels contributed to development of our vaccine [21, 32, 100, 103, 121–122]. In our ongoing clinical trial [NCT04458545; 107] efforts to characterize B cell activity as a potential biomarker of vaccine response is therefore an important aim.

An effective vaccine for OUD would confer notable advantages and function as a valuable adjunct to existing treatments. As stated, though there are several FDA-approved medications for treating OUD, medication adherence and retention in treatment remain critical challenges with estimates suggesting that 50–75% of patients entering treatment for OUD drop out of treatment within the first year [123–125]. This places individuals with OUD who relapse at high risk of opioid overdose [10], especially in light of a growing presence of HPSOs in illicit drug supplies. An effective, multivalent opioid vaccine could confer long-lasting protection from overdose among individuals with OUD at risk for relapse. Unlike other approved medications for OUD, vaccines do not require detoxification prior to their use, do not pose a risk of misuse or diversion, and because of their high specificity, appear unlikely to have cross-reactivity with other off-target opioids. Therefore, an opioid vaccine could effectively be integrated into ongoing treatment with methadone, buprenorphine, or naltrexone. Unlike treatment with oral methadone or sublingual/buccal formulations of buprenorphine, vaccination would not require daily dosing to confer protection. Another potential application for opioid vaccines is use in individuals who use opioids recreationally, and are therefore not candidates for medications like methadone, buprenorphine, or naltrexone. Furthermore, recent estimates suggest that individuals who use psychostimulants like cocaine and amphetamines may be at risk of opioid-related overdose due to contamination of stimulants with HPSOs [2]. Individuals who primarily use these psychostimulants are not tolerant to opioids and are therefore at risk of overdose should they inadvertently use stimulants adulterated with an HPSO [6]. Still, more work would be needed to explore the utility and acceptability of an opioid vaccine in this population. As discussed, disadvantages of vaccines for OUD lie in the potential for variable antibody response, the need for several doses over time, and thus far unclear onset and

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duration of action. Ongoing and future clinical trials testing opioid vaccines must address these questions in order to offer a promising and effective therapeutic option.

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List of Abbreviations

APC	Antigen Presenting Cell
BBB	Blood Brain Barrier
CDC	Centers for Disease Control and Prevention
FDA	Food and Drug Administration
HPSO	High-Potency Synthetic Opioids
IgG	Immunoglobulin G
mAb	Monoclonal Antibodies
OUD	Opioid Use Disorder
SUD	Substance Use Disorders
VLP	Virus Linked Particles

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Article highlights

- Vaccines and immunotherapies offer some advantages as standalone and adjuvant interventions for opioid use disorder [OUD]
- Extensive preclinical data support current candidate vaccines for OUD
- Further work is needed to extend preclinical findings to clinical trials, and efforts to address prior Substance Use Disorder [SUD] vaccine shortcomings are important

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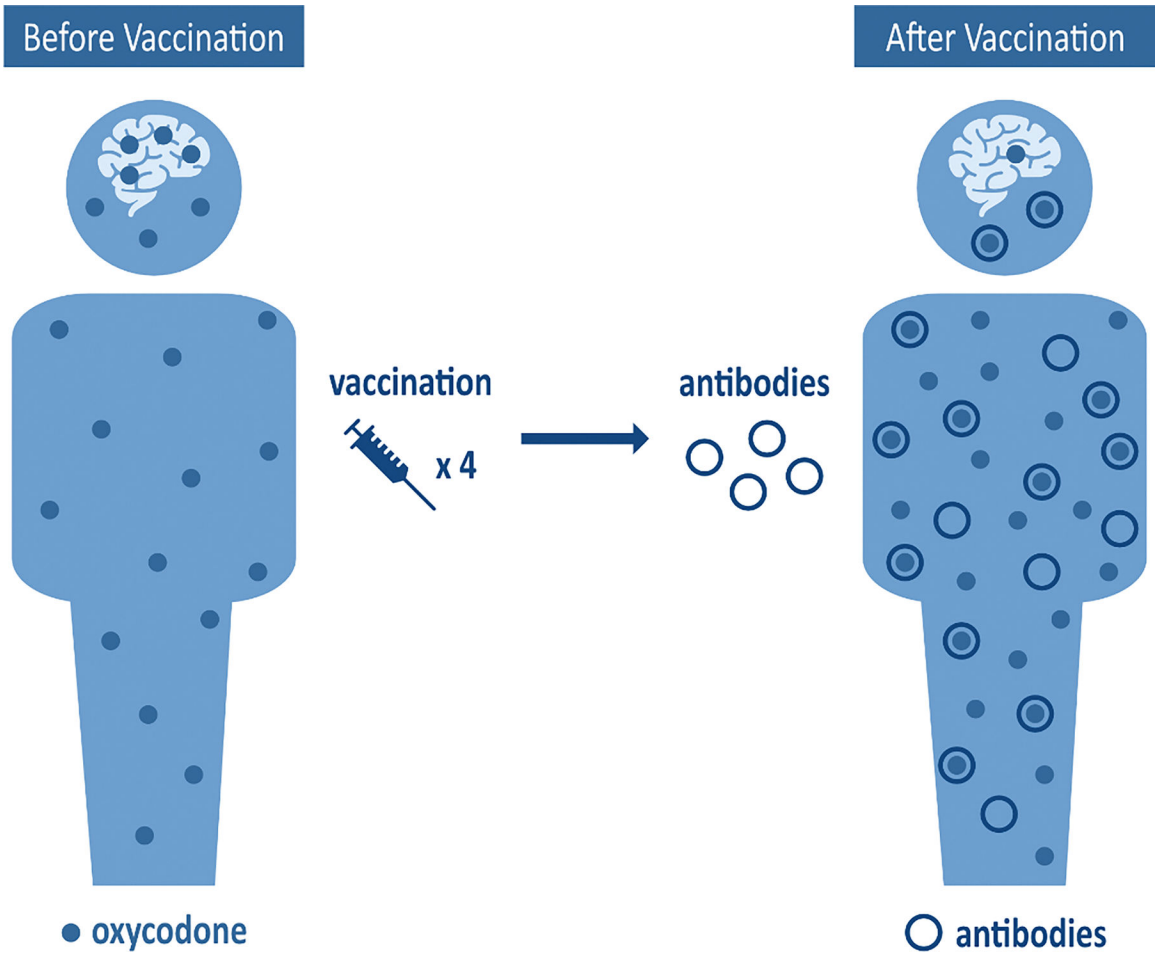

Figure 1:
Oxycodone Vaccine Mechanism

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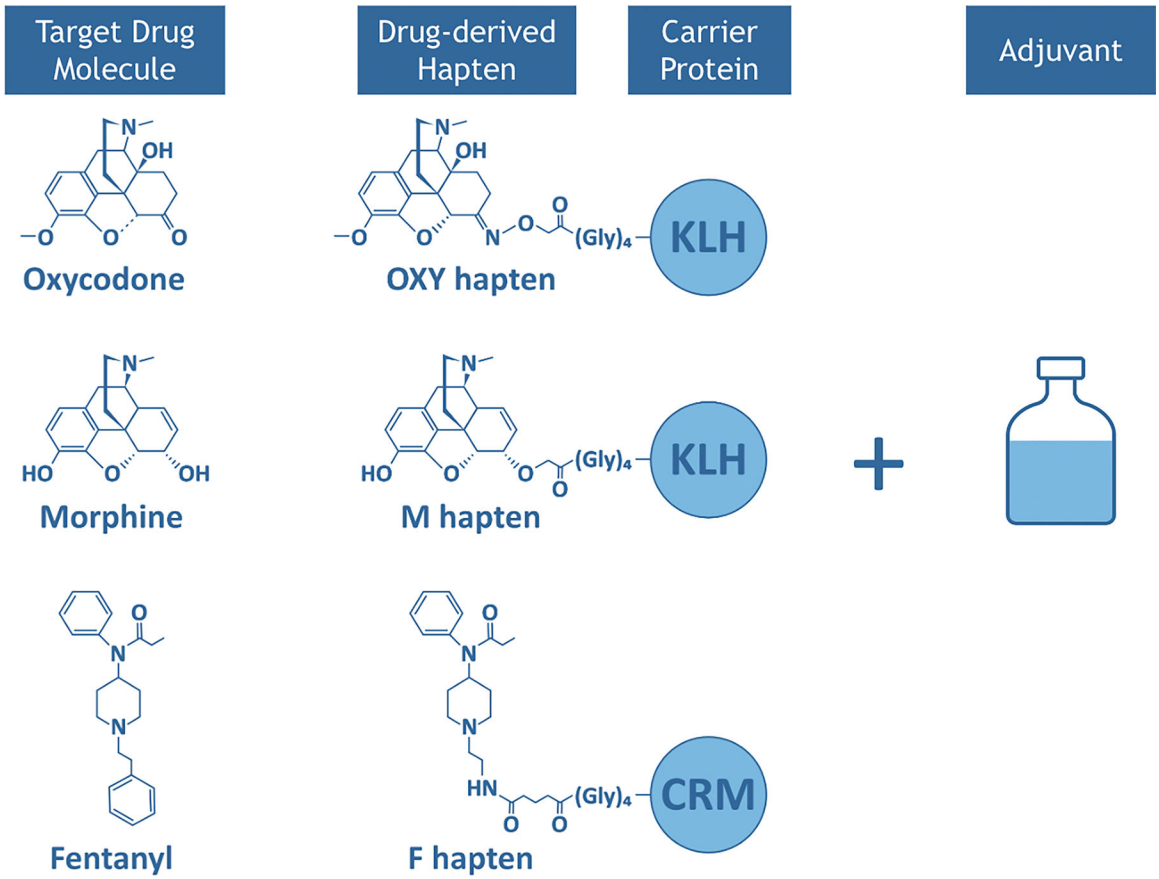

Figure 2:
Substance Use Disorder (SUD) Vaccine Components