HHS Public Access

Author manuscript

Expert Opin Investig Drugs. Author manuscript; available in PMC 2023 June 06.

Published in final edited form as:

Expert Opin Investig Drugs. 2023 March ; 32(3): 181–185. doi:10.1080/13543784.2023.2187286.

The potential role of opioid vaccines and monoclonal antibodies in the opioid overdose crisis

Suky Martinez[a], **Hannah Harris**[a], **Thomas Chao**[b], **Rachel Luba**[a], **Marco Pravetoni**[c], **Sandra D Comer**[a], **Jermaine D Jones**[a]

[a]Division on Substance Use Disorders, Columbia University Irving Medical Center & New York State Psychiatric Institute, New York, NY, USA

[b]Behavioural Reward Affect + Impulsivity Neuroscience Lab, Faculty of Medicine, the University of British Columbia, Vancouver, Bc, Canada

[c]Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA, USA

Keywords

Opioids; overdose; opioid vaccines; monoclonal antibodies; immunotherapies

1. The need for continued development of medications to treat opioid overdose

Since the late 1990s, the U.S. has experienced an exponential increase in opioid-related overdose deaths and made substantial economic expenditures to address the harms associated with opioid use disorder (OUD) [1,2]. As the epidemic has evolved, we have observed a substantial increase in the detection of potent, illicitly manufactured fentanyls in opioid drug supplies as well as in cocaine and methamphetamine drug supplies, and within counterfeit pills sold as oxycodone, benzodiazepines, and other prescription drugs. This has led to increases in the rates of opioid-related overdose among those with OUD and among those who are not traditionally at risk such as psychostimulant users and recreational

CONTACT Suky Martinez, suky.martinez@nyspi.columbia.edu, Division on Substance Use Disorders, Columbia University Irving Medical Center, New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032, USA.

Declaration of interests

Within the past three years, JD Jones received compensation (in the form of partial salary support) and has served as a paid consultant to Alkermes and the World Health Organization. Within the past three years, SD Comer has received research funding from Alkermes, BioXcel Therapeutics, Corbus, Go Medical, Intra-cellular Therapies, Janssen, and Lyndra. SD Comer has also consulted for: Alkermes, Clinilabs, Opiant, and Otsuka, and she has received honoraria from the World Health Organization. SD. Comer is also the recipient of NIH funding to study opioid vaccines and monoclonal antibodies. M Pravetoni has filed patents disclosing the composition and methods of use of vaccines and monoclonal antibodies for substance use disorders. Dr. Pravetoni is also the recipient of NIH funding to study opioid vaccines and monoclonal antibodies.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

non-opioid drug users (i.e. individuals who may not meet criteria for a substance use disorder) [3].

The development of novel evidence-based treatments remains a key focus of the U.S. Food and Drug Administration (FDA)'s efforts to address the opioid epidemic [4]. Two strategies that are known to reduce the morbidity and mortality associated with opioid overdose are the use of naloxone (and nalmefene) to reverse an acute overdose and maintenance on FDA-approved medications, such as methadone, buprenorphine, and naltrexone [5]. The currently available FDA-approved medications for opioid overdose and OUD largely exact their therapeutic effects via the mu-opioid receptor [6]. However, rates of fatal opioid overdose remain high. Therefore, the development of novel therapeutics is a public health priority.

2. Using vaccines and monoclonal antibodies to target opioid overdose

A research area that is gaining traction for treating substance use disorders is the development of immunotherapies, which first began in the 1970s [7]. Opioid vaccines activate the immune system to create antibodies that selectively bind to a targeted opioid. By preventing the passage of drugs across the blood-brain barrier, or other target organs, opioid-specific antibodies attenuate the pharmacological effects of opioids [8]. Preclinical studies have demonstrated that opioid vaccines are highly specific to their target drug (i.e. oxycodone, morphine, fentanyl), and demonstrate the ability of vaccines to reduce the abuse potential of opioids in various models (e.g. conditioned place-preference, drug self-administration) [9–12]. Importantly, preclinical models have shown that opioid-specific antibodies can prevent opioid-induced respiratory depression, the primary means by which opioid over-intoxication becomes fatal [13,14]. Active immunization with vaccines, however, typically requires multiple injections over several weeks so this approach is not feasible for treating acute opioid overdose. However, if antibody production produced by vaccination is robust and long-lasting, vaccination could prevent an overdose from occurring or re-occurring in patients who relapse to illicit opioid use.

Another immunotherapeutic approach to treating opioid overdose is passive immunization with monoclonal antibodies (mAbs) that target specific opioids. Like the antibodies that are produced through active immunization with a vaccine, mAbs bind and sequester opioid drug molecules in the serum and other organs, which prevents them from entering the central nervous system [15]. Monoclonal antibodies are primarily produced from antigen-specific B cell lymphocytes via several techniques including hybridoma technology, phage display, and cloning and expression of antibody binding domains as recombinant monoclonal antibodies [15]. One of the potential advantages of mAbs is their rapid onset of action and ability to bind opioids after a single administration [16]. Therefore, mAbs could be useful for reversing an acute opioid overdose. If the mAb is long-lasting, this approach also could prevent an opioid overdose. One recent study in rodents found that the administration of mAbs successfully reversed fentanyl-induced respiratory depression, antinociception, and bradycardia for up to a week [17]. Other rodent studies from independent groups also show the preclinical efficacy of anti-opioid mAbs and the viability of chimeric or humanized mAbs against opioids [15,16,18,19]. In sum, preclinical findings in these rodent models

suggest that opioid vaccines and monoclonal antibodies have significant potential in the treatment of opioid overdose.

3. Clinical considerations

3.1. Preclinical to clinical translation

The translation of robust preclinical findings into promising results in human trials is where most treatments fail in the medication development pipeline [20]. Similar to opioid vaccines, preclinical studies of nicotine and cocaine vaccines demonstrated the ability to attenuate the abuse potential of nicotine and cocaine [21–26]. Unfortunately, subsequent clinical trials yielded disappointing results. One of the issues was significant variability in antibody levels post-vaccination. In many of these studies, less than one-third of vaccinated participants developed sufficient antibody levels to produce a good clinical response [27]. Furthermore, it could take a month or longer and require repeated vaccine injections to establish a therapeutic immune response [22].

3.2. Key pharmacokinetic factors affecting clinical outcomes

Two clinical studies have been published to date on a morphine vaccine [28,29]. The investigators reported dose-dependent increases in antibody levels and no serious medication-related adverse effects [29]. However, no treatment-related outcomes were reported so questions remain regarding the efficacy of immunotherapy in humans with OUD. For example, the optimal schedule of inoculations, the needed frequency of boosters, the ideal range and onset/offset of antibody titers needed to produce a clinically meaningful medication effect, and the interindividual variability in antibody titers are critical but unanswered clinical questions.

3.3. Risk of attempts to override the effects of opioid vaccines/mAbs

An additional concern is the possibility of individuals attempting to override the vaccine's therapeutic effect by taking larger doses of the target opioid, potentially exposing them to additional overdose risk. Data from other therapeutics, however, suggest that this is more a theoretical than an actual concern. Prior studies of the competitive opioid antagonist naltrexone found attempts to override the blockade occurred infrequently suggesting that the high cost of larger doses of the opioid of choice may serve as a sufficient barrier to continued opioid use [30]. This study, paired with clinical evidence supporting naltrexone's efficacy, suggests that it is unlikely that individuals would frequently attempt to override the antagonist effects of naltrexone, which may extend to blockade induced by opioid vaccines.

3.4. Risk of 'opioid-switching'

The risk of 'opioid-switching' by individuals who use opioids illicitly is also a clinical concern. For example, a primary oxycodone user may initiate heroin or fentanyl use if a vaccine or mAb targeting oxycodone blocks the pharmacological effects of oxycodone. Because vaccines/mAbs are so selective for the target opioid, a multivalent vaccine/mAb approach that targets multiple opioids makes the most sense clinically from the perspective of both safety and effectiveness for the treatment of both opioid overdose and OUD.

3.5. Implications for pain management

Whether and how opioid vaccines/mAbs could affect standard medical practices, such as pain management, is also an important consideration. For example, the introduction of an opioid vaccine/mAb would require clinicians to be aware of their patient's opioid vaccination status in order to select the most efficacious opioids for pain management. This could become challenging if an individual is vaccinated against the same opioid selected by their clinician for pain management and alternatives are not readily available. Factors such as regional differences in the availability of certain opioids could worsen some of these issues and lead to unintended health disparities.

3.6. Stand-alone versus adjunctive treatment

One important issue with opioid vaccine treatments is the context and potential application of their use. The introduction of an opioid vaccine could be implemented as an adjunct to the current standards of care (e.g. vaccination + naltrexone, methadone, or buprenorphine). In this proposed approach, the vaccine would target the illicit opioid, like heroin, while not affecting the function of a maintenance opioid, like buprenorphine. As such, the potential benefits of the immunotherapy would be additive to that of the OUD medication. This approach is a departure from previous vaccine development attempts, especially the psychostimulant vaccines, where there are no FDA-approved medications. Opioid immunotherapies could also be used as stand-alone treatments for OUD, should clinical trials demonstrate robust effects on treatment outcomes. An immunotherapeutic treatment may be preferable in situations where pharmacotherapy is not ideal or desired by the patient, or for long-term stabilization after traditional pharmacotherapy is phased out.

3.7. Implications for medication compliance

One of the most promising advantages of opioid immunotherapy is the possibility of increased medication compliance, an issue that plagues all forms of OUD treatment [31]. The frequency of lapses, relapses, and discontinuation of pharmacotherapy presents a serious challenge for the successful management of OUD, as well as increasing the vulnerability to overdose [5]. Immunotherapy may provide individuals who are experiencing a relapse episode with an additional layer of protection against overdose while they reengage in traditional pharmacotherapy and psychotherapy.

3.8. Implications for treatment of users of non-opioid drugs

Finally, opioid immunotherapy could have novel indications related to overdose risk mitigation. Opioid vaccines could be offered to individuals who may not meet criteria for OUD but are at risk of opioid overdose. For example, vaccination against fentanyl could serve as an overdose risk mitigation strategy for individuals who use cocaine and methamphetamine, whose risk of unintentional fentanyl exposure has risen in recent years.

4. Expert opinion

To fully understand the clinical potential of opioid immunotherapy, additional clinical research is needed in several areas. In addition to safety and tolerability evaluations, data on the immunogenicity (e.g. heterogeneity in immune response) of opioid vaccines is crucial

to assessing their efficacy, implementation, and planned indications for use. These issues have significantly stifled the development of vaccine therapies for other substance use disorders. Preclinical data suggest opioid vaccines and monoclonal antibodies may not only yield improved outcomes in the treatment of OUD but also provide a novel and innovative overdose mitigation strategy. However, these promising findings have yet to be replicated in clinical samples, which is not a given, as preclinical studies do not always predict effectiveness in clinical trials. Furthermore, a comprehensive treatment strategy for OUD would likely necessitate multivalent vaccines/mAbs targeting several opioids. Just as the opioid epidemic transitioned from prescription opioids to heroin and then fentanyl, new non-fentanyl opioids have already begun to emerge in the illicit market [32]. Multivalent vaccines or monoclonal antibodies could allow immunotherapies to adapt to a changing drug market. Yet more preclinical and clinical research is needed on efficacy and safety. Finally, given the concerns that individuals have expressed concerning other types of vaccines (e.g. COVID-19 vaccines), research is needed to understand the acceptability, appropriateness, and feasibility of this approach in different subgroups of people who use drugs to inform implementation strategies. It is critical to have these discussions not only with diverse samples of individuals with OUD but also clinicians to ensure all risks and viewpoints are understood.

Despite the promise of opioid vaccines and monoclonal antibodies, several scientific and ethical considerations warrant mentioning. The implementation of opioid vaccination therapy may lead to an ongoing ‘cat-and-mouse game’ between vaccine developers and illicit drug manufacturers. This may result in new, more dangerous opioids entering the illicit drug market. Finally, individuals with substance use disorders and their treatment historically have often been entrenched in punitive approaches in the U.S., particularly among individuals from minority backgrounds. Thus, concerning vaccine/mAb therapy, vigorous ethical debate should be conducted regarding the potential use of this therapeutic approach to safeguard the self-determination and autonomy of individuals who use drugs.

One of the main goals of the development of opioid immunotherapies is to provide an effective treatments for OUD and/or overdose prevention. These treatments may have the ability to serve as a stand-alone or adjunctive treatment to the currently available interventions. Although the development of immunotherapies may be promising, it is critical to remember that this research is still in its early stages. As such, it is difficult to predict exactly how the development of opioid immunotherapies evolve in the future with certainty or precision. However, if this research continues to show effectiveness in the progression from animal to human studies, there are novel and impactful real-world applications. For example, it may be possible to identify individuals who are at high risk of developing OUD and use immunotherapies to prevent the development or progression of severe addiction. Similarly, immunotherapies could be used as a overdose mitigation strategy to reduce overdose risk among those not interested in OUD treatment, or in cases of treatment-refractory OUD. Additionally, it is possible that the large-scale implementation of an efficacious immunotherapy could reduce the overall demand for opioids.

The availability of a opioid vaccine or monoclonal antibody therapy could become a standard of care, and could be included in evidence-based guidelines for OUD and overdose

prevention. Nonetheless, it is important to note that many unanswered questions remain, and more research is needed to fully understand their potential indications and impact. More specifically, studies including clinical trials, are needed to determine the safety, efficacy, and long-term impact of these treatments, as well as their cost-effectiveness compared to current treatments. Moreover, any changes to treatment guidelines would need to consider barriers to the widespread adoption of these immunotherapies, including regulatory approval, reimbursement, and availability of the treatments.

There are also other challenges in the development of opioid immunotherapies worth mentioning, specifically variability in response to the intervention. Prior research with nicotine and cocaine vaccines, suggests some individuals may respond well to opioid immunotherapies, while others may not, which would complicate the implementation of this treatment approach. Taken together, the development of opioid immunotherapies has the potential to greatly impact the current and future opioid epidemic . As evidence is still emerging, the authors have exercised caution in making proclamations concerning the potential of opioid vaccines and monoclonal antibodies in the opioid overdose crisis. Although the development of opioid immunotherapies presents notable challenges, novel treatment approaches are needed given the now decades-long opioid crisis. Opioid immunotherapy may present a novel treatment and overdose risk mitigation strategy with a larger target audience, in comparison to currently available approaches.

Funding

The development of this manuscript was not funded. S Martinez and R Luba are supported by the National Institute on Drug Abuse grant T32DA007294.

List of Abbreviations

FDA	Food and Drug Administration
OUD	Opioid Use Disorder

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Villani J, Ganoza L, Sims BE, et al. Substance use prevention research funded by the NIH. Drug Alcohol Depend 2020;206.
2. O'Donnell J, Tanz LJ, Gladden RM, et al. Trends in and characteristics of drug overdose deaths involving illicitly manufactured fentanyls — United States, 2019–2020. MMWR Morb Mortal Wkly Rep 2021;70:1740–1746. [PubMed: 34914673]
3. Twillman RK, Dawson E, LaRue L, et al. Evaluation of trends of near-real-time urine drug test results for methamphetamine, cocaine, heroin, and fentanyl. JAMA Network Open 2020;3:e1918514. [PubMed: 31899527] • Provides robust data indicating the increased prevalence of fentanyl in the psychostimulant supply.
4. United States Food and Drug Administration. Overdose prevention framework [Internet] United States Food and Drug Administration. 2022 [cited 2022 Jan 9]. Available from: https://www.fda.gov/media/160381/download.

5. Bell J, Strang J. Medication treatment of opioid use disorder. Biol Psychiatry 2020;87:82–88. [PubMed: 31420089] • Provides an overview of the strengths and weaknesses of the current medications to treat opioid use disorder.
6. Sofuoglu M, DeVito EE, Carroll KM. Pharmacological and behavioral treatment of opioid use disorder. Psychiatr. res. clin. pract 2019;1:4–15.
7. Bonese KF, Wainer BH, Fitch FW, et al. Changes in heroin self-administration by a rhesus monkey after morphine immunisation. Nature 1974;252:708–710. [PubMed: 4474602]
8. Pravetoni M, Comer SD. Development of vaccines to treat opioid use disorders and reduce incidence of overdose. Neuropharmacology 2019;158:107662. [PubMed: 31173759] • Provides an concise review of immunotherapeutic strategies for opioid use disorder.
9. Han Y, Cao L, Yuan K, et al. Unique pharmacology, brain dysfunction, and therapeutic advancements for fentanyl misuse and abuse. Neurosci Bull 2022;38:1365–1382. [PubMed: 35570233]
10. Pravetoni M, Pentel PR, Potter DN, et al. Effects of an oxycodone conjugate vaccine on oxycodone self-administration and oxycodone-induced brain gene expression in rats. PLoS One 2014;9: e101807. [PubMed: 25025380]
11. Pravetoni M, le Naour M, Harmon TM, et al. An Oxycodone conjugate vaccine elicits drug-specific antibodies that reduce oxycodone distribution to brain and hot-plate analgesia. J Pharmacol Exp Ther 2012;341:225–232. [PubMed: 22262924]
12. Townsend EA, Blake S, Faunce KE, et al. Conjugate vaccine produces long-lasting attenuation of fentanyl vs. food choice and blocks expression of opioid withdrawal-induced increases in fentanyl choice in rats. Neuropsychopharmacology 2019;44:1681–1689. [PubMed: 31043682]
13. Eubanks LM, Blake S, Natori Y, et al. A highly efficacious carfentanil vaccine that blunts opioid-induced antinociception and respiratory depression. ACS Chem Biol 2021;16:277–282. [PubMed: 33533592]
14. Raleigh MD, Peterson SJ, Laudenbach M, et al. Safety and efficacy of an oxycodone vaccine: addressing some of the unique considerations posed by opioid abuse. PLoS One 2017;12: e0184876. [PubMed: 29194445]
15. Hicks D, Baehr C, Silva-Ortiz P, et al. Advancing humanized monoclonal antibody for counteracting fentanyl toxicity towards clinical development. Hum Vaccin Immunother [Internet] 2022;18. 10.1080/21645515.2022.2122507.
16. Smith LC, Bremer PT, Hwang CS, et al. Monoclonal antibodies for combating synthetic opioid intoxication. J Am Chem Soc 2019;141:10489–10503. [PubMed: 31187995]
17. Baehr CA, Wu MM, Pandit SG, et al. Pharmacological profiling of antifentanyl monoclonal antibodies in combination with naloxone in pre- and postexposure models of fentanyl toxicity. J Pharmacol Exp Ther 2022;381:129–136. [PubMed: 35153198]
18. Rodarte J, Baehr C, Hicks D, et al. Structures of drug-specific monoclonal antibodies bound to opioids and nicotine reveal a common mode of binding [Internet]. Structure 2023;31:20–32.e5. https://linkinghub.elsevier.com/retrieve/pii/S0969212622004579 [PubMed: 36513069]
19. Ban B RC B, Oertel T, et al. Novel chimeric monoclonal antibodies that block fentanyl effects and alter fentanyl biodistribution in mice. MAbs [Internet] 2021;13. 10.1080/19420862.2021.1991552.
20. Jones JD, Varshneya NB, Hudzik TJ, et al. Improving translational research outcomes for opioid use disorder treatments [Internet]. Curr Addict Rep 2021;8:109–121. 10.1007/s40429-020-00353-5 • Provides a review of the issues faced in the preclinical to clinical transition of treatments for opioid use disorder.
21. Fraleigh NL, Oliva R, Lewicky JD, et al. Assessing the immunogenicity and toxicity of the AFPL1-conjugate nicotine vaccine using heterologous and homologous vaccination routes. PLoS One 2019;14:e0221708. [PubMed: 31442285]
22. Hall W, Gartner C. Ethical and policy issues in using vaccines to treat and prevent cocaine and nicotine dependence. Curr Opin Psychiatry 2011;24:191–196. [PubMed: 21430537]
23. LeSage MG, Keyler DE, Pentel PR. Current status of immunologic approaches to treating tobacco dependence: vaccines and nicotine-specific antibodies. AAPS J 2006;8:E65–E75. [PubMed: 16584135]

24. Lindblom N, de Villiers SHL, Kalayanov G, et al. Active immunization against nicotine prevents reinstatement of nicotine-seeking behavior in rats. Respiration 2002;69:254–260. [PubMed: 12097770]

25. Moreno AY, Azar MR, Warren NA, et al. A critical evaluation of a nicotine vaccine within a self-administration behavioral model. Mol Pharm 2010;7:431–441. [PubMed: 20104903]

26. Pentel PR, Malin DH, Ennifar S, et al. A Nicotine Conjugate Vaccine Reduces Nicotine Distribution to Brain and Attenuates Its Behavioral and Cardiovascular Effects in Rats. Pharmacol Biochem Behav 2000;65:191–198. [PubMed: 10638653]

27. Truong TT, Kosten TR. Current status of vaccines for substance use disorders: a brief review of human studies. J Neurol Sci 2022;434:120098. [PubMed: 34952345]

28. Akbarzadeh A, Norouzian D, Farhangi A, et al. Immunotherapy of 347 volunteer outpatient morphine addicts by human therapeutic morphine vaccine in Kermanshah province of Iran. J. Pharmacol. Toxicol 2008;4:30–35.

29. Akbarzadeh A, Norouzian D, Farhangi A, et al. Study of human therapeutic morphine vaccine: safety and immunogenicity. Asian J Biochem 2006;2:58–65.

30. Sullivan MA, Bisaga A, Mariani JJ, et al. Naltrexone treatment for opioid dependence: does its effectiveness depend on testing the blockade? Drug Alcohol Depend 2013;133:80–85. [PubMed: 23827259]

31. Fishman M, Vo HT, Burgower R, et al. Treatment trajectories during and after a medication trial for opioid use disorder: moving from research as usual to treatment as usual [Internet]. J Addict Med 2020;14:331–336. 10.1097/ADM.0000000000000592 [PubMed: 31972765]

32. Center for Forensic Science Research and Education. NPS opioids in the United States- trend report Q1 and Q2, 2021 cited 2023 FEB 12. From: https://extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.npsdiscovery.org/wp-content/uploads/2022/04/2022-Q1_NPS-Opioids_Trend-Report.pdf

Article highlights

- Immunotherapies may present a novel approach to help address the evolving opioid overdose crisis
- Preclinical data suggest that opioid vaccines and monoclonal antibodies have therapeutic potential
- More research, specifically in humans, is needed to demonstrate the efficacy and safety of immunotherapies for opioid use disorder and better understand potential implementation barriers