



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

## Science &amp; Society

Lessons from COVID-19  
to increase opioid  
vaccine acceptance

Roxana Damiescu,<sup>1</sup>  
Mita Banerjee,<sup>2</sup>  
Norbert W. Paul,<sup>3</sup> and  
Thomas Efferth <sup>1,\*</sup>

**COVID-19 has put vaccine efficacy under a spotlight. However, the reluctance of people to be vaccinated has postponed the end of the COVID-19 pandemic. Currently, opioid vaccines are being developed, which could help prevent opioid addiction, overdoses, or relapse in combination with medication-assisted therapy. The fear is that the uptake of opioid vaccines could be met by the same reluctance as seen with COVID-19 vaccines.**

**Opioid use disorder**

Although pharmaceutical opioids have been responsible for triggering an opioid epidemic, most opioid overdose deaths now involve illicitly manufactured fentanyl and fentanyl analogs. Currently available therapies include naloxone, to prevent opioid overdose, and medication-assisted treatment (MAT) (methadone and buprenorphine) combined with behavioral therapies to treat opioid use disorder (OUD). However, the risk of relapse remains, because of neurobiological changes associated with opioid use.

Restrictive measures taken worldwide in response to the coronavirus disease 2019 (COVID-19) pandemic, such as social isolation and lockdown, have negatively impacted the general population. However, those with OUD have been

particularly affected (Box 1)<sup>ii</sup>, not only because social isolation is often associated with increased mental health problems [1], but also because of limited access to appropriate treatment during lockdown.

**Opioid vaccination: a new hope**

Opioid overdose is a common cause of admission to intensive care units (ICUs), with symptoms of opioid overdose including respiratory depression, miosis, and loss of consciousness. Naloxone is administered as an antidote and mechanical ventilation is often necessary. In addition, patients who are opioid dependent usually experience opioid-induced hyperalgesia, and central sensitization or tolerance, making pain management even more difficult and resulting in symptoms of acute opioid withdrawal. In patients with OUD and opioid tolerance, multimodal analgesia is necessary to properly manage pain, including nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, tricyclic antidepressants, and anticonvulsants (gabapentin), combined with nonpharmacological interventions. In addition, to suppress opioid withdrawal symptoms,  $\alpha_2$  adrenergic agonists (e.g., clonidine and dexmedetomidine) or NMDA receptor antagonists (e.g., ketamine) can be administered [2].

The drastic increase in opioid overdose deaths over the past year is an indirect call for help to find a solution for opioid addiction. In the USA, various opioid-specific vaccines are being developed, including oxycodone and hydrocodone, morphine, heroin, fentanyl, and fentanyl analogs. In animal studies, vaccines reduced the distribution of the opioid of interest to the brain, preventing euphoric effects or respiratory depression, the main cause of death after opioid overdose; in addition, the vaccines did not interact with available opioid MATs. The long half-life of the antibodies produced could help prevent a possible relapse, giving the brain time to

recover [3]. Given the positive results obtained in preclinical studies, the National Institutes of Health (NIH) is funding the first Phase 1a/1b clinical trial (NCT04458545)<sup>iii</sup> of the oxycodone vaccine, which contains oxycodone-based hapten (OXY) conjugated to a keyhole limpet hemocyanin (KLH) carrier protein<sup>iii</sup>. The safety, immunogenicity, and efficacy of OXY-KLH will be determined in volunteers, who are active opioid users<sup>iii</sup>. The development, optimization, and approval of opioid vaccines require further research, and even once approved, they will still have some limitations and might not be suitable for all patients. However, they could provide a powerful tool against drug addiction and protect professionals at risk of exposure (e.g., healthcare professionals, first responders, and military personnel). However, the hesitancy seen with COVID-19 vaccine uptake suggests that opioid vaccine hesitancy might also be an issue following the approval of the latter.

**SARS-CoV-2 vaccination among people with substance use disorder**

Patients with substance use disorder (SUD) are at risk of developing more severe forms of COVID-19 and a worse outcome because of associated comorbidities [4]. The risk is especially high for patients with OUD followed by tobacco and alcohol use disorder.

Although COVID-19 vaccines have been shown to be safe, there are still numerous individuals who remain unvaccinated. There are various reasons for the reluctance to get vaccinated, including distrust in the safety of the vaccine, confidence that an infection may not be that severe, or a general distrust of governments and healthcare systems. In one study of people with SUD, 45% were happy to be vaccinated, whereas over 40% of the individuals questioned were either unwilling to get vaccinated or were undecided [5].

### Box 1. The evolution of the opioid epidemic

In the USA, opioids are the main cause of drug overdose deaths. Pharmaceutical opioids were responsible for triggering the opioid crisis and, since 2013, the main opioid involved has been illicit fentanyl or its analogs, either alone or in combination with other drugs (e.g., amphetamines and cocaine). Given the high number of people misusing and addicted to opioids, the opioid crisis was declared a public health emergency in 2017. Since the beginning of the COVID-19 pandemic, the number of drug overdose deaths in the USA has dramatically increased, surpassing 100 000 deaths as of January 2022 (Figure 1).

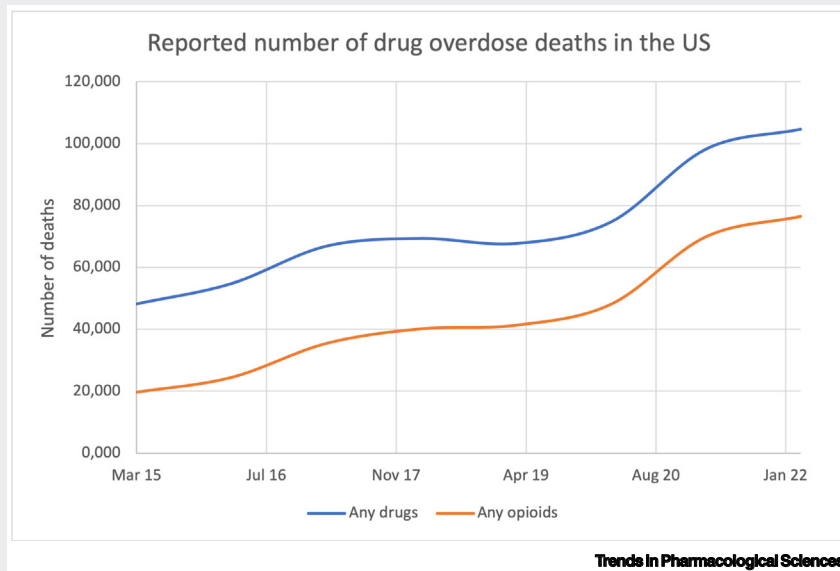


Figure 1. Provisional drug overdose death counts. Source: National Center for Health Statistics.

To assure easier access to the COVID-19 vaccine among patients with SUD, various strategies have been implemented<sup>iv</sup>. Nevertheless, despite such efforts, studies have shown that only ~50% of patients with SUD are willing to get vaccinated, a percentage that was even lower among various minority communities [5]. The reasons for this unwillingness include distrust in the government and pharmaceutical industry, and the perceived lack of safety of the vaccines. However, people tend to trust their doctors and the medical decisions they make, showing the important role that healthcare providers have in raising awareness and providing proper information regarding the benefits of vaccination [5].

Following the spread of the omicron strain and its different subtypes, the risk of breakthrough infection was significantly

higher (22.5% hospitalization risk and a 1.6% fatal outcome) in fully vaccinated patients with SUD compared with those without SUD [6]. This indicates that patients with SUD remain at a higher risk of COVID-19 infection and, thus, that safety measures have a key role in preventing the spread of the virus.

### Concluding remarks and future perspectives

Given the collision of the COVID-19 pandemic and opioid epidemic, preliminary data showed that patients with OUD and those chronically treated with opioids were at a higher risk of hospitalization and negative outcomes following COVID-19 [7]. Under these extreme circumstances, the role of healthcare professionals in increasing vaccine awareness is crucial. In addition, in an era when

disinformation, fake news, and social media have such a significant influence on the decision around whether to get vaccinated, researchers, governments, and the media need to learn about the importance of appropriate, accurate communication with the target populations. Scientists need to have more of a presence on social media and explain the benefits of vaccination in a way that is accessible for the general population (e.g., via short videos or interviews) and that counteracts vaccine disinformation. This would also mean that different professionals at risk of exposure, but without a medical background, could access and understand the information provided, which might increase their vaccine acceptance. Governments should learn from the COVID-19 pandemic, improve their communication and collaboration with healthcare professionals, and avoid sending mixed messages regarding their position on vaccines. Additionally, governments should ensure proper supplies and easy access to opioid vaccines for people with OUD, once they are approved for clinical use.

Moreover, there are vulnerable communities that distrust the healthcare system as a whole, but do trust healthcare professionals (e.g., physicians, pharmacists, etc.) that they already know. These communities might be a good starting point to better understand some of the reasons behind vaccine refusal.

If opioid vaccines are approved, healthcare professionals nationwide should be provided with the necessary material to inform patients about opioid vaccination and clarify any questions or concerns that they might have. Nongovernmental organizations could also be involved and organize information campaigns in affected communities. Additionally, opioid vaccines could also positively impact the daily life of functioning drug users and patients with OUD, because the long half-life of antibodies combined with MAT could prevent relapse and improve working and social life (Table 1). Last but

Table 1. Vaccine deployment

Problems with COVID-19 vaccines	Possible solutions for future vaccines
<ul style="list-style-type: none"> <li>• Distrust in vaccine efficacy</li> </ul>	<ul style="list-style-type: none"> <li>• Share information regarding efficacy, side effects, and possible interactions</li> </ul>
<ul style="list-style-type: none"> <li>• Concerns regarding side effects</li> </ul>	<ul style="list-style-type: none"> <li>• Improve communication between scientists, governments, and groups of interest</li> </ul>
<ul style="list-style-type: none"> <li>• Disinformation (fake news)</li> </ul>	<ul style="list-style-type: none"> <li>• Reach out to affected communities</li> </ul>
<ul style="list-style-type: none"> <li>• Distrust in government and pharmaceutical industry</li> </ul>	<ul style="list-style-type: none"> <li>• Involve social media through videos, interviews, or information campaigns</li> </ul>
<ul style="list-style-type: none"> <li>• Initial limited access and availability</li> </ul>	<ul style="list-style-type: none"> <li>• Ensure easy access and proper supply of necessary doses</li> </ul>

not least, opioid vaccines could also protect professionals at risk of exposure.

The high percentage of individuals with OUD who are not willing to be given the COVID-19 vaccine raises the question of whether they would be willing to receive an opioid vaccine, once one is available in the clinic [5]. Since COVID-19 infections can have the same deadly outcome in patients with OUD as seen with opioid overdoses, the reasons behind vaccine refusal remain obscure. If eligible patients with OUD are willing to be treated with an opioid vaccine, research to understand the motives behind their acceptance could also reveal reasons for the reluctance to be treated with COVID-19 vaccines.

### Acknowledgments

The authors are grateful to a PhD stipend of the Deutsche Forschungsgemeinschaft (DFG GRK2015/2) to R.D.

### Declaration of interests

The authors declare no conflict of interest.

### Resources

<sup>i</sup>[www.samhsa.gov/medication-assisted-treatment](http://www.samhsa.gov/medication-assisted-treatment)

<sup>ii</sup>[www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm](http://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm)

<sup>iii</sup><https://beta.clinicaltrials.gov/study/NCT04458545?patient=opioid%20use%20disorder%20vaccine&locStr=&distance=0>

<sup>iv</sup>[www.addictionpolicy.org/post/initiative-to-get-covid-19-vaccines-to-people-with-substance-use-disorder](http://www.addictionpolicy.org/post/initiative-to-get-covid-19-vaccines-to-people-with-substance-use-disorder)

<sup>1</sup>Department of Pharmaceutical Biology, Institute of Pharmaceutical and Biomedical Sciences, Johannes Gutenberg University, Staudinger Weg 5, Mainz, Germany

<sup>2</sup>Department of English and Linguistics, American Studies, Johannes Gutenberg University, Mainz, Germany

<sup>3</sup>Institute for History, Philosophy, and Ethics of Medicine, Johannes Gutenberg University Medical Center, Mainz, Germany

\*Correspondence:  
[effe@uni-mainz.de](mailto:effe@uni-mainz.de) (T. Efferth).

<https://doi.org/10.1016/j.tips.2022.08.010>

© 2022 Elsevier Ltd. All rights reserved.

### References

1. Henry, B.F. *et al.* (2020) COVID-19, mental health, and opioid use disorder: old and new public health crises intertwine. *Psychol. Trauma Theory Res. Pract. Policy* 12, S111–S112
2. Karamchandani, K. *et al.* (2018) Critical care pain management in patients affected by the opioid epidemic: a review. *Ann. Am. Thorac. Soc.* 15, 1016–1023
3. Pravetoni, M. and Comer, S.D. (2019) Development of vaccines to treat opioid use disorders and reduce incidence of overdose. *Neuropharmacology* 158, 107662
4. Wang, Q.Q. *et al.* (2021) COVID-19 risk and outcomes in patients with substance use disorders: analyses from electronic health records in the United States. *Mol. Psychiatry* 26, 30–39
5. Mellis, A.M. *et al.* (2021) Trust in a COVID-19 vaccine among people with substance use disorders. *Drug Alcohol Depend.* 220, 108519
6. Wang, L. *et al.* (2021) Increased risk for COVID-19 breakthrough infection in fully vaccinated patients with substance use disorders in the United States between December 2020 and August 2021. *World Psychiatry* 21, 124–132
7. Qeadan, F. *et al.* (2021) Opioid use disorder and health service utilization among COVID-19 patients in the US: a nationwide cohort from the Cerner Real-World Data. *eClinicalMedicine* 37, 100938