

## LETTER TO THE EDITOR

## Immunotherapy for opioid use disorder treatment. An innovative approach to the fentanyl crisis

*Inmunoterapia para el tratamiento del trastorno por consumo de opioides.  
Una estrategia innovadora frente a la crisis por fentanilo*

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Dear Editor:



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The opioid crisis is a growing social and public health issue<sup>1</sup> that had caused the death from overdose of about 125 000 people worldwide by 2019.<sup>2,3</sup>

This crisis began in the 1990s, when the prescriptions of opioids for pain management steadily increased without considering their addictive potential and the risks associated with their use. Moreover, the crisis was exacerbated by overprescription, lack of education about pain management, and the lack of adequate regulation and surveillance.<sup>4</sup> Since then, four waves of opioid-related mortality have occurred: the first was characterized by deaths caused by overdoses with opioid analgesics; the second, by an increase in the number of deaths related to heroin use; the third, by an increase in the use of fentanyl and its synthetic analogs; and the fourth, by the massive use of fentanyl in combination with other stimulant drugs such as methamphetamines and cocaine, which has dramatically increased the number of overdoses and deaths.<sup>4</sup> While the United States, the world's leading country in fentanyl use in 2021 with 19.3%, is currently the country most affected by this surge<sup>4</sup> with record numbers of deaths from overdose,<sup>5</sup> this situation has extended to other countries and regions such as Australia, New Zealand, and Europe.<sup>4</sup>

The goal of opioid use disorder treatment is to improve physical and mental state, reduce the risk of overdose, and help prevent criminal behavior. In that regard, there are several approaches to rehabilitation and maintenance of patients with this disorder, including cognitive-behavioral and educational interventions as part of rehabilitation, psychological support as part of maintenance programs, and pharmacological interventions, such as opioid replacement therapy, involving the substitution of a problematic opioid for a safer one under medical supervision to reduce the side effects of opioid withdrawal.<sup>3</sup>

Moreover, although the standard treatment for opioid overdose, particularly fentanyl at present, involves the use of  $\mu$ -opioid receptor antagonists such as naloxone and naltrexone, these antagonists have limitations despite their effectiveness.<sup>6</sup> Consequently, an innovative but controversial solution has been proposed: using monoclonal antibodies and preparations or "vaccines" designed to block the access of opioids to the central nervous system, thus preventing their recreational and harmful effects.<sup>6</sup> This strategy has a solid molecular basis since, by generating a specific immune response against narcotic substances such as opioids, such "vaccines" attempt to impede the passage of these substances through the blood-brain barrier, preventing their psychotropic effects and thus reducing the risk of addiction and overdose.<sup>6</sup>

However, this strategy is not exempt from problems to be addressed. For example, the extrapolation of the results of vaccines against the abuse of substances such as nicotine

or cocaine in animal models to humans is a problem yet to be solved since, despite their success in animal models, these vaccines have not proven to be effective in human clinical trials.<sup>7,8</sup> In addition, there are several ethical and social dilemmas, which include whether these vaccines should be offered preventively, to whom, and if this strategy could limit access to legitimate analgesic treatments in previously immunized individuals. Finally, there are also a number of important technical challenges to overcome before these vaccines are approved for clinical use, such as the durability of immune response, the need for multiple doses or boosters, and the emergence of fentanyl derivatives that are not affected by the immune response elicited by these vaccines.<sup>8</sup>

Despite the above, immunotherapy against opioid use disorder is a research line that could contribute significantly to overcoming the current opioid crisis, which focuses mainly on fentanyl abuse, as it has a real potential to reduce the risk of addiction and overdose due to these substances. However, besides confirming its pharmacological feasibility, the medical and scientific community must also evaluate and resolve the ethical and social implications of its possible implementation. For the time being, it is essential to strengthen comprehensive approaches to the treatment and rehabilitation of these patients, not only concentrating on pharmacological therapy, but also on the implementation of timely educational and cognitive-behavioral interventions and adequate social and psychological support.

### Conflicts of interest

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