



Commentary

Stronger, longer, better opioid antagonists? Nalmefene is NOT a naloxone replacement

Alexander F. Infante^{a,*}, Abigail T. Elmes^a, Renee Petzel Gimbar^a, Sarah E. Messmer^b, Christine Neeb^c, Jennie B. Jarrett^a

^a Department of Pharmacy Practice, College of Pharmacy, University of Illinois Chicago, 833 South Wood St (MC 886), Chicago, IL 60612, United States

^b Department of Medicine, College of Medicine, University of Illinois Chicago, Westside Research Office Building, 1747W Roosevelt Rd, Rm 256, Chicago, IL 60608, United States

^c Division of Internal Medicine, School of Medicine, University of Colorado, Academic Office Building 1, 12631 E 17th Ave, Aurora, CO 80045, United States



ARTICLE INFO

Keywords:

Nalmefene
Naloxone
Opioid overdose
Opioid antagonists

ABSTRACT

The fatal overdose crisis claims nearly 200 lives daily in the United States (U.S). Evolutions in the illicit drug supply, such as the addition of sedative adulterants and a shift to synthetic opioids such as fentanyl, have driven increasing rates of both fatal and non-fatal overdose. Specifically, synthetic opioid usage of fentanyl was implicated in 68 % of the U.S. drug overdose deaths in 2022 alone. This has placed tremendous burden on communities, emergency medical services, and healthcare systems, and contributed to tragedy and grief both in the U.S. and worldwide. Despite the availability of effective opioid antagonist medications and standards of care, there has been increased interest in research and development of alternative opioid overdose reversal agents by the National Institutes of Health (NIH) in partnership with pharmaceutical manufacturers over the last decade. The U.S. Food and Drug Administration (FDA) recently approved nalmefene (Opvee) a mu-opioid receptor antagonist that boasts an extended half-life and stronger mu-receptor affinity compared to the standard of care use of naloxone for opioid reversal. In this article, we explore the medical need and ramifications of the introduction of longer-acting opioid antagonists in the current opioid overdose landscape. Existing data highlight the effectiveness of already available naloxone products as a safe and effective standard of care. These data support the notion that stronger, longer-acting agents may be unnecessary, and their existence may cause undue harm, such as more severe and/or prolonged withdrawal symptoms, lead to challenging patient interactions, and complicate the initiation of medications for opioid use disorder. More evidence is needed before healthcare professionals should implement the use of stronger, longer-acting opioid antagonists for reversing opioid overdose over evidence-based, cost-effective naloxone.

Introduction

As the fatal overdose crisis rages on, claiming nearly 200 lives daily in the United States (U.S.) alone, the medical community is scrambling to research and develop new tools to aid those affected. (Centers for Disease Control & Prevention, 2021) Evolutions in the drug supply, such as the addition of various adulterants and a shift to synthetic opioids, drive the research for these new tools while simultaneously sparking debate on their utility and need. (Centers for Disease Control & Prevention, 2021; Hill et al., 2022; Volkow & Collins, 2017) Synthetic opioids, such as fentanyl and its analogs, are standard within the illicit drug supply, and increasingly dangerous adulterants, such as xylazine,

further complicate our ability to combat the fatal overdose crisis. (Hill et al., 2022; Skolnick, 2022) New animal data suggests that xylazine acts as an agonist at the kappa opioid receptor, suggesting it may be susceptible to reversal via naloxone, however this is unfounded and not supported in human data or clinical practice. (Bedard et al., 2023) Over the last decade, these synthetic opioids have become progressively implicated for the rising rates of opioid overdose deaths, contributing to over 68 % of the opioid overdose deaths in 2022. (Kariisa et al., 2023) The increasing mortality rate only tells part of the story, with 6.4 to 8.4 times as many non-fatal opioid overdoses occurring each year in the U.S. (Skolnick, 2022) This places tremendous burden on emergency medical services as well as the healthcare system as a whole. (Skolnick, 2022)

* Corresponding author.

E-mail address: ainfan4@uic.edu (A.F. Infante).

<https://doi.org/10.1016/j.drugpo.2024.104323>