Reemergence of Carfentanil: A Growing Threat in the U.S. Opioid Crisis

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Carfentanyl, a highly potent synthetic opioid originally used as a tranquilizer for large animals, is re-emerging as a significant public health threat in the U.S[1–3]. The recent sevenfold increase in overdose deaths with carfentanil detected (from 29 in early 2023 to 238 in mid-2024) suggests a rapid resurgence. Unlike the 2016–2017 outbreak, which was localized and had low illegally manufactured fentanyl (IMF) co-detection rates (<25%), the current wave spans 37 states with 87% IMF co-detection, indicating a broader and more integrated presence in the illicit drug supply.[4]

While fentanyl has been a major driver of overdose deaths — accounting for a 4.86% increase in synthetic opioid fatalities from 71,238 in 2021 to 74,702 in 2023[5,6] — carfentanyl poses an even greater risk due to its potency, being 100 times more potent than fentanyl and 10,000 times more than morphine[7,8]. Due to its potency and low concentrations in biological samples, forensic detection of carfentanil relies on liquid chromatography-tandem mass spectrometry (LC-MS/MS), gas chromatography-mass spectrometry (GC-MS), and high-resolution mass spectrometry (HRMS)[9]. Blood, urine, and postmortem tissues are analyzed, as carfentanil metabolizes rapidly. With rising illegally manufactured fentanyls (IMFs), laboratory refine detection protocols to enhance accuracy and prevent misinterpretation.[10]

Carfentanyl's reappearance poses numerous challenges. Its potency makes it difficult to detect and regulate in the drug market, and users often unknowingly consume it when it is mixed with other substances[9,11]. A dose as small as a grain of salt can be lethal, creating a heightened risk for overdose and overdose deaths[10]. Also, carfentanyl endangers first responders, who may unintentionally come into contact with the drug during emergencies[12], thus, highlighting the need for advanced protective measures and training for emergency personnel.

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Moreover, the resurgence of carfentanyl could worsen the ongoing opioid crisis by adding to the already dangerous drug landscape – the opioid crisis/epidemic[11]. The opioid crisis in the U.S. began in the 1990s with the widespread overprescription of opioid painkillers, driven by pharmaceutical claims of low addiction risk[13,14]. This led to a rise in prescription opioid misuse, followed by tightened regulations, which pushed many users towards heroin. By the 2010s, the crisis escalated with the influx of illicitly manufactured synthetic opioids (IMFs), particularly fentanyl and its analogs such as carfentanil, which are far more potent and lethal. In recent years, the opioid crisis in the U.S. has shifted from prescription opioids to illicitly manufactured synthetic opioids, with fentanyl and its analogs particularly, carfentanyl, driving a surge in overdose deaths[15–17]. As public awareness and enforcement efforts targeted fentanyl, drug traffickers might have begun turning to more potent alternatives including carfentanyl, which can be produced and transported in smaller quantities with far deadlier consequences[18].

To address the growing threat of carfentanyl, surveillance of drug market must be strengthened, and coordination between law enforcement and public health agencies enhanced to disrupt supply chains and detect carfentanyl early. Naloxone, a life-saving antidote for opioid overdoses[19], must be expanded, especially in high-risk areas, as reversing carfentanyl overdoses typically require higher doses[20,21]. Education campaigns targeting drug users and the public about the risks of synthetic opioid contamination are necessary for promoting safer behaviors and overdose preparedness. Harm reduction programs, including syringe exchanges should be enhanced to promote safer drug use practices among people who inject drugs.

The re-emergence of carfentanyl has potential to worsen the U.S. opioid crisis and demands immediate and coordinated action to curtail its deadly impact in particular among the economically deprived rural communities[22], where limited healthcare access, high unemployment, and social isolation heighten vulnerability[22]. These regions have higher overdose rates due to increased synthetic opioid infiltration and scarce addiction treatment resources[22]. Immediate, coordinated action is crucial to mitigate its deadly impact on these populations.

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