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Review Article

Historical perspectives and emerging trends in fentanyl use: Part 2 – overdose and misuse

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Abstract

The misuse of fentanyl and its analogs has significantly worsened the opioid crisis, leading to a sharp increase in overdose fatalities. Fentanyl overdose primarily causes severe respiratory depression, which can result in hypoxia, cardiac arrest, and death, often exacerbated by co-intoxication. Additionally, the opioid in question can induce chest wall rigidity, further complicating treatment procedures. Despite international control efforts, the drug's high potency and low cost have fueled its widespread trafficking, including in counterfeit pills. While naloxone is the primary antidote, its effectiveness is limited, highlighting the need for stronger, long-acting treatments. Factors such as polypharmacy, prescription misuse, and environmental exposure – as well as the potential for fentanyl's use as a chemical weapon – pose significant public safety risks. In conclusion, addressing the current wave of the opioid crisis requires a comprehensive approach, integrating treatment solutions, prevention, and harm reduction strategies.

Keywords

fentanyl, naloxone, opioids, overdose, toxicity

Introduction

Synthetic opioid design aims to develop more potent analgesics with improved safety profiles compared to natural compounds. Paradoxically, several of these agents have recently been implicated in thousands of deaths worldwide. A prominent example is fentanyl, a 4-anilidopiperidine derivative used in the management of severe pain and surgical anesthesia, which, along with its analogs, has intensified the opioid crisis to unprecedented levels (Stanley 2014; Han et al. 2019). Unfortunately, despite concerted efforts by national and international authorities to curb its illicit use, trafficking and acute overdose cases have surged (Suzuki and El-Haddad 2016; Frank and Pollack 2017).

The United States is currently experiencing one of several waves of the opioid crisis, with highly potent synthetic opioids playing a dominant role (Bresler and Sinha 2021; Manchikanti et al. 2022). Unfortunately, this issue is escalating at an alarming rate in Canada and across the European continent (Fischer et al. 2024). The illicit fentanyl market appears to be sustained primarily through two mechanisms: clandestine manufacturing and the diversion of pharmaceutical products from the regulated supply chain (Mounteney et al. 2015). Another alarming trend is the rising number of overdose cases, often involving individuals unknowingly consuming fentanyl-containing substances – often in lethal doses (McGowan et al. 2018; Jacka 2020).

Clinically, opioid intoxication is marked by respiratory depression, which can lead to hypoxia, hypercarbia, and death (Dolinak 2017). For over half a century, naloxone, a primary antidote, has been used to treat such cases, achieving a high survival rate when administered in appropriate doses (Fairbairn et al. 2017; Moss and Carlo 2019). However, in the face of rising synthetic opioid misuse, new challenges have emerged in the management of overdose. Numerous reports of fatal fentanyl-related cases suggest the need for multiple naloxone administrations, raising concerns about its efficacy and safety. Ongoing investigations are examining whether inadequate antidote dosing, pharmacokinetic limitations, or pharmacodynamic characteristics of fentanyl and its analogs contribute to these issues (Elkiweri et al. 2009; Lynn and Galinkin 2018). Additionally, concerns over fentanyl and its analogs as potential chemical weapons have driven researchers to explore novel strategies for managing acute opioid poisoning. In this context, the present study also examines recent research on the use of more potent and long-acting antidotes in the management of acute opioid poisoning, as well as strategies for reducing opioid misuse and its associated consequences.

The aim of the present review is to synthesize recent findings on fentanyl toxicity, patterns of misuse, and new approaches to reducing mortality and overdose scenarios. It is anticipated that this will prove advantageous for healthcare practitioners, researchers, and law enforcement agencies, each of which holds a vested interest in alleviating the adverse impacts on public health.

Methods

For this review, data were collected and analyzed from leading scientific databases, including PubMed, ScienceDirect, and Google Scholar, to access the latest peer-reviewed literature, as well as from ResearchGate for additional sources on fentanyl toxicity and the challenges associated with the treatment of fentanyl overdose. Additionally, official reports from authoritative regulatory bodies, such as the European Monitoring Centre for Drugs and Drug Addiction, the United Nations Office on Drugs and Crime, the Centers for Disease Control and Prevention, the Drug Enforcement Administration, Health Canada, and others, were reviewed. These sources were utilized to develop a comprehensive synthesis of current toxicological insights and trends in synthetic opioid abuse.

Results and discussion

Scope and trends of fentanyl abuse

Although fentanyl has an established role in human medicine, its safety continues to be a subject of scrutiny. The primary concerns surrounding the drug are its high potency, the potential for addiction and abuse, and the associated risk of fatal overdose (Walter 2023; Karunarathna 2024; European Monitoring Centre for Drugs and Drug Addiction 2025). As a result, fentanyl has been under international control since 1964 (United Nations Office on Drugs and Crime 2016, 2017).

The first large-scale outbreak of fatal fentanyl-related incidents occurred in the United States (US) in the 1980s. During this period, fentanyl was illicitly synthesized and sold as a heroin substitute or mixed with other drugs, leading to a sharp increase in overdose deaths. This issue spread to Europe a decade later (Han et al. 2019). A second wave of fentanyl abuse was documented in 2006, when the US again experienced a spike in fentanyl-related fatalities (Algren et al. 2013). By this time, established patterns of recreational use had emerged, resulting in more than a twofold increase in mortality (Han et al. 2019). Recent data from the United Nations Office on Drugs and Crime (UNODC) SMART program (Synthetics Monitoring: Analyses, Reporting, and Trends) indicate a renewed sharp increase in opioid-related overdose deaths, predominantly in North America and, to a lesser extent, Europe (United Nations Office on Drugs and Crime 2017). Between 2012 and 2016, the number of overdose deaths in the United States attributed to synthetic opioids rose from 2,628 to 20,145, marking a more than sevenfold increase and signaling the onset of the third wave of the opioid crisis (Centers for Disease Control and Prevention 2017a; Socías and Wood 2017; United Nations Office on Drugs and Crime 2017). A newly released report by the National Center for Health Statistics, which analyzed 64,000 drug overdose deaths, found that fentanyl accounted for more unintentional fatalities than any other drug (31%) (Centers for Disease Control and Prevention 2017b). Canada has similarly faced an unprecedented overdose epidemic, with British Columbia declaring a public health emergency in 2016 (Health Canada 2022).

Today, illicit fentanyl is primarily supplied through two routes: clandestine manufacturing and the diversion of pharmaceutical-grade fentanyl from the regulated supply chain (Mounteney et al. 2015). Its pharmacological properties offer distinct advantages for traffickers, as its potency far exceeds that of traditional opioids. This enables comparable narcotic effects with substantially smaller quantities and reduces production costs (United Nations Office on Drugs and Crime 2017; Han et al. 2019). This enhances concealment, thereby lowering legal risks for traffickers. In the US, it is estimated that the demand for opioids could be met by substituting the approximately 50 metric tons of heroin currently consumed with only a few tons of fentanyl (Kilmer et al. 2022). Consequently, wholesale prices declined by half between 2016 and 2021, increasing affordability for end-users. The improvements in fentanyl synthesis methods, aided by publicly available scientific publications and patents, have also streamlined the illicit production of the drug, which often involves the use of uncontrolled precursors. Another notable trend is the increasing use of fentanyl as an additive in other drugs, such as heroin and cocaine, replacing traditional adulterants like caffeine, procaine, sugar, and tranquilizers. Regrettably, consumers are often unaware of this, exposing them to severe health risks (United Nations Office on Drugs and Crime 2023).

According to the US National Forensic Laboratory Information System, reports of fentanyl (both pharmaceutical and illicitly produced) rose from 4,697 in 2014 to over 117,045 in 2020 (Drug Enforcement Administration 2022a). An unclassified document from the Drug Enforcement Administration (DEA) indicates that China remains the primary source of fentanyl and related substances, with production also increasing in Mexico and India (Drug Enforcement Administration 2020). The DEA reported that in 2021, nearly 20.4 million counterfeit pills and close to 7,000 kg of fentanyl powder were seized (The White House 2022). According to Lyman and Hart, DEA-reported amounts of fentanyl seized represent only 1/10 to 1/20 of the total amount trafficked in the US (Lyman and Hart 2023). Thus, given that 2 mg of fentanyl is lethal when administered acutely, this quantity corresponds to billions of lethal doses, theoretically enough to provide a fatal dose to every member of the US population (The White House 2022).

In North American opioid markets, fentanyl is increasingly found in combination with unregulated benzodiazepines, xylazine, and veterinary tranquilizers. Illicitly produced fentanyl is also sold as a stand-alone product in various forms, including injectable powder, substances for smoking or inhalation, and tablets or combined with other substances in counterfeit pills designed to resemble legitimate pharmaceuticals (Moss and Carlo 2019). Through its „One Pill Can Kill“ campaign, the DEA warns Americans of the pervasive trafficking of counterfeit pills resembling prescription medications such as OxyContin®, Percocet®, and Xanax®. In 2022, the agency reported that 6 out of 10 counterfeit pills contained a lethal dose of fentanyl (Drug Enforcement Administration 2022b). Later in 2023, laboratory analyses revealed that 7 out of 10 seized pills contained a fatal dose, and the DEA projects similar trends in fentanyl distribution through 2024 (Drug Enforcement Administration 2024).

Currently, synthetic opioids occupy a relatively minor role in the European drug market. However, according to the European Monitoring Centre for Drugs and Drug Addiction, this may change in the future. In 2023, the UNODC reported a 95% decrease in opium production in Afghanistan. As a result, the availability of heroin is expected to decrease, which could create favorable conditions for increased abuse of synthetic opioids on the old continent. Therefore, Europe also needs to strengthen its readiness to deal with the challenges that market change may bring (European Monitoring Centre for Drugs and Drug Addiction 2024). The data show that fentanyl and 3-methylfentanyl are produced illegally mainly in countries bordering the European Union (EU) and subsequently trafficked to neighboring European countries. Reports from recent years suggest that these substances are marketed under names such as “fentanyl,” “China white,” “white heroin,” or simply “heroin” in several European countries—including, for example, Bulgaria, which has faced heroin shortages (Mounteney et al. 2015). The 2023 European Drug Report states that fentanyl seizures in the EU included 2.7 kilograms of powder, 168 liters of liquid fentanyl (including one seizure in Bulgaria), and 8,435 fentanyl tablets (European Monitoring Centre for Drugs and Drug Addiction 2024).

The diversion of fentanyl-containing drugs from the regulated supply chain has a long history (Stanley 2014). In fact, from the 1970s to the 1980s, prior to the emergence of illegal production and abuse, fentanyl was used for non-medical purposes by clinicians (anesthesiologists and surgeons) with access to it (Armenian et al. 2018). Subsequently, the various methods of application exacerbated the issue (Boyer 2012). Diversion methods for fentanyl-containing medications include inappropriate or excessive prescribing by clinicians, theft from pharmacies, collection of waste from hospitals and geriatric wards, sale of unused patches by patients or their relatives, abuse and trafficking by healthcare professionals, including anesthesiologists and nurses, and the use of multiple or fraudulent prescriptions by patients (Mounteney et al. 2015). The diversion of fentanyl-containing drugs primarily affects transdermal patches, from which the active substance can be extracted into a liquid and injected, placed in a glass container, heated and inhaled, smoked using foil, applied to the skin, or cut into pieces to be sucked or swallowed. Discarded fentanyl patches can also be misused, as they retain 28%–84% of the original dose even after 72 hours of use (Marquardt et al. 1994). Lozenges, sublingual tablets, and fentanyl infusion solutions are less commonly abused (Drug Enforcement Administration 2022a). Consequently, the International Narcotics Control Board collects and reports international data on the legal distribution of fentanyl for medical and scientific purposes, which is presented as fentanyl consumption data per capita (Mounteney et al. 2015).

Fentanyl overdose: Clinical presentation and exposure factors

Fentanyl overdose represents an exacerbation of its side effects. Similar to other opioids, it induces pupil constriction (miosis), although this sign may be less reliable in severe cases due to co-intoxication (Boyer 2012). Patients may present with confusion, stupor, or coma depending on the severity of the overdose. Documented complications include acute pulmonary syndrome, compartment syndrome, hypothermia, rhabdomyolysis, renal failure, aspiration pneumonia, and post-hypoxic leukoencephalopathy (Suzuki and El-Haddad 2016). Fentanyl acts on the central nervous system‘s respiratory centers, causing a reduction in respiratory volume. At higher serum concentrations, this can progress to apnea, hypoxemic or hypercarbic respiratory failure, cardiac arrest, and death (Pattinson et al. 2009; Dolinak 2017). Respiratory depression typically peaks within 5 minutes post-administration, with an average recovery time of 4 hours in humans (Magosso et al. 2004; Han et al. 2019). Non-cardiogenic pulmonary edema associated with opioid overdose likely arises from neurogenic mechanisms, involving both hemodynamic and inflammatory responses. These lead to vasoconstriction, increased pulmonary hydrostatic pressure, and enhanced capillary permeability (Baumann et al. 2007). Hypoxemia from respiratory depression can result in cyanosis, particularly around the lips and extremities. Co-intoxication with substances such as antipsychotics, ethanol, anticonvulsants, and sedative-hypnotics further exacerbates respiratory depression and lowers the threshold for its onset (Sorg et al. 2016; Powell and Peters 2019). Polypharmacy is frequently implicated in fentanyl-related fatalities, underscoring the necessity for thorough toxicological analysis. Interactions between fentanyl and co-toxicants contribute significantly to its lethality, highlighting the importance of understanding pharmacodynamic interactions in overdose management.

Fentanyl overdose, along with that of its analogs, exhibits an atypical and potentially fatal feature not commonly observed with other opioids such as morphine or heroin: chest wall rigidity, also referred to as “wooden chest syndrome.” This condition develops rapidly, typically within approximately two minutes of intravenous administration, and can persist for up to 15 minutes. Notably, doses lower than those required to induce respiratory depression are sufficient to trigger this response (Streisand et al. 1993; Torralva and Janowsky 2019). The syndrome is characterized by laryngospasm and rigidity of the chest wall and diaphragm muscles. While chest wall rigidity is likely mediated by enhanced activation of α-adrenergic receptors in the brainstem, the development of laryngospasm is thought to involve both adrenergic and cholinergic mechanisms (Pergolizzi et al. 2021). These adverse effects contribute significantly to respiratory distress, impede the restoration of ventilation, and markedly increase mortality risk (Dolinak 2017).

Opioid-related fatalities affect individuals across genders, races, and nearly all age groups (Althoff et al. 2020). However, certain conditions heighten susceptibility to opioid toxicity. Factors such as positional asphyxia (*e.g.*, lying face-down against a soft surface) or suffocation due to awkward neck positioning can severely restrict airflow through the upper airways. Additionally, physiological reserves and the ability to mitigate the toxic effects of opioids are diminished in elderly individuals or those with pre-existing conditions, including pulmonary diseases, congestive heart failure with pulmonary edema, obstructive sleep apnea, or obesity (Dolinak 2017). The risk of death in opioid overdose increases during sleep due to the absence of conscious respiratory drive and the heightened vulnerability to disruptions in chemoreceptor activity, which regulate respiratory rhythm. Moreover, the upper airways are more susceptible to stenosis during sleep, a risk exacerbated by aging (Pattinson 2008). Particular vigilance is warranted if the patient exhibits snoring, as this may signal impending upper airway obstruction in sedated individuals. In such cases, positioning the patient on their side is crucial, as this promotes patency of the collapsible oropharyngeal tissues (Ong et al. 2011).

Although less common, fentanyl overdose can occur in individuals using prescription fentanyl products, particularly when misused or taken in excessive doses. For instance, misuse of fentanyl patches (e.g., by heating or oral ingestion) or of transmucosal formulations such as lozenges or sprays increases overdose risk, especially when diverted for recreational use (Dowell et al. 2017; Schepis et al. 2019). However, a significant proportion of fentanyl overdoses in recent years has been associated with the illicit drug market. Fentanyl is often mixed with other substances, including heroin, cocaine, or methamphetamines – often without the user’s knowledge. This practice greatly amplifies overdose risk, as users remain unaware of fentanyl’s markedly higher potency (Cance et al. 2003; Carroll et al. 2017; Nir 2021; Bass et al. 2022; McKnight et al. 2023). A study by Kenney et al. (2018) revealed that two-thirds of individuals tested for drug use were positive for fentanyl, despite claiming no prior exposure (Kenney et al. 2018). Recent analyses have identified three key differences in the effects of fentanyl compared to heroin, as reported by individuals with substance use disorders. Fentanyl produces a more explosive onset of a powerful opioid effect (“rush”), has a shorter duration of action (typically 1–2 hours), and exhibits significantly higher potency. Users have also reported adverse effects such as sudden respiratory distress, blurred vision, and numbness in the back of the head and neck (Ciccarone et al. 2017). Critically, fentanyl overdose progresses much more rapidly than that of heroin. Fatal respiratory depression can develop in under five minutes following fentanyl exposure, whereas heroin overdose typically results in death at least 20 minutes post-use. This stark contrast in the onset and progression of toxicity underscores the heightened danger of fentanyl, particularly when unknowingly consumed by individuals accustomed to less potent opioids such as heroin (Darke and Duflou 2016; Carroll et al. 2017).

Involuntary exposure to fentanyl can occur during professional duties, particularly among emergency responders, healthcare workers, and law enforcement personnel. The greatest physiological risk stems from exposure to aerosolized fentanyl, as the drug rapidly enters systemic circulation via the nasal and pulmonary routes. To mitigate this risk, the use of specialized filter masks is recommended (Lyman and Hart 2023). Concerns about overdose through dermal absorption have also been raised, given that fentanyl is a stable, lipophilic molecule resistant to degradation at room temperature or under sunlight (Beletsky et al. 2020). However, the American College of Medical Toxicology and the American Academy of Clinical Toxicology state that significant opioid toxicity is unlikely to result from dermal contact with fentanyl in forms such as tablets, powders, or solutions. In cases where absorption does occur, toxicity is not expected to develop rapidly, allowing sufficient time for medical intervention. Nonetheless, further experimental data are needed to fully elucidate these risks. For routine handling of fentanyl or cleaning of contaminated surfaces, nitrile or latex gloves provide adequate skin protection (Moss et al. 2017). Surface decontamination can be effectively achieved using oxidizing agents in bleach solutions containing chlorine, adjusted to a lower pH, which degrade over 95% of the opioid within one hour of contact (Oudejans et al. 2021). While accidental ocular exposure is not generally fatal or a significant concern, it can be prevented by using full-face respirators (Moss et al. 2017).

Environmental exposure to fentanyl and its analogs can also occur when these substances are employed as chemical incapacitating agents. Research into their use for this purpose dates back to the 1990s, when the US Department of Defense explored fentanyl derivatives as potential non-lethal weapons. However, the inability to establish a safe threshold – an optimal incapacitating dose without lethal consequences – led to the abandonment of these efforts (Tin et al. 2021). Similar initiatives were pursued by the Russian military, culminating in the 2002 Dubrovka Theater incident in Moscow (Pilch and Dolnik 2003; Pearson 2006). During this operation, an aerosol mixture of carfentanil and remifentanil through the ventilation system to incapacitate Chechen terrorists holding hostages was deployed. Tragically, over 120 hostages died, and more than 650 survivors required hospitalization (Pilch and Dolnik 2003; Wax et al. 2003; Riches et al. 2012; Patocka et al. 2024). The relatively simple and cost-effective synthesis of fentanyl and its analogs not only contributes to their abuse as illicit drugs but also raises concerns about their potential use as chemical weapons. In the hands of terrorists, these substances could pose a substantial threat to public safety (Pearson 2006; Riches et al. 2012; Tin et al. 2021). Currently, naloxone remains the primary pharmacological countermeasure for opioid poisoning. However, its short duration of action (typically no more than two hours) limits its effectiveness in mass casualty incidents involving ultra-potent, long-acting synthetic opioids. This underscores the urgent need for the development of more potent, longer-acting antidotes for opioid agonist poisoning (Wax et al. 2003).

Management of fentanyl overdose

The rapid and potent effects of fentanyl necessitate an urgent, systematic approach to patient assessment and timely therapeutic interventions (Boyer 2012; Powell and Peters 2019). Emergency resuscitation in cases of opioid intoxication primarily focuses on addressing cardiopulmonary arrest caused by airway obstruction and respiratory failure. Thus, maintaining airway patency and adequate ventilation in patients with respiratory depression or imminent arrest is the highest priority (Dezfulian et al. 2021). For patients with a Glasgow Coma Scale (GCS) score below 15 and a respiratory rate of fewer than 10–12 breaths per minute, immediate administration of supplemental oxygen is essential (Bouillon et al. 2003; Ramos-Matos et al. 2024). Concurrently, preparations should be made for the prompt administration of an opioid antagonist, such as naloxone, to counteract the effects of fentanyl without delay (Armenian et al. 2018).

Respiratory depression is the leading cause of death in opioid overdose. Given its mechanism of action, the μ-opioid receptor antagonist naloxone has been employed as a global antidote since the 1960s (Kim and Nelson 2015; Krieter et al. 2016). Due to its extensive first-pass metabolism in the liver, naloxone is not administered orally. Intravenous administration produces effects within approximately two minutes, while intranasal or intramuscular administration achieves similar outcomes within about 10 minutes (Kerr et al. 2009; Boyer 2012). Alternative delivery methods include subcutaneous, endotracheal (for intubated patients), inhalation, sublingual, and buccal routes (Kim and Nelson 2015). Traditionally, naloxone administration was restricted to trained healthcare professionals. The intensifying opioid crisis has led to the approval of over-the-counter naloxone products, enabling at-risk individuals to self-administer the antidote or receive assistance from those nearby (Strang and Farrell 1992; Lyman and Hart 2023). While concerns persist about whether unrestricted access may inadvertently promote risky drug use behaviors, intramuscular auto-injectors and nasal spray devices, including higher-dose formulations, have been approved for public distribution to enhance timely intervention in opioid overdoses (Kim et al. 2009; Lynn and Galinkin 2018).

Naloxone exhibits a rapid blood-brain transfer (approximately 6.5 minutes), comparable to that of fentanyl and its analogs (Saari et al. 2024). Its half-life is relatively short, around 60 minutes, although individual variations range from 30 minutes to 90 minutes (Scheuermeyer et al. 2018). When administered to patients with acute opioid intoxication or opioid dependence, naloxone may precipitate the so-called acute opioid withdrawal syndrome. This occurs in approximately 1–2% of patients and can present as mild behavioral disturbances, such as agitation, a strong craving for opioids, piloerection, vomiting, hypertension, tachycardia, and/or aggression. Severe reactions, including seizures and other life-threatening conditions, are also possible. The likelihood of these reactions is higher in individuals with opioid tolerance and a history of chronic opioid abuse (Lynn and Galinkin 2018; Moss and Carlo 2019). Despite these potential complications, the administration of naloxone should not be delayed, as its benefits outweigh the risks (Buajordet et al. 2004; Belz et al. 2006; Wermeling 2015; Lynn and Galinkin 2018). In this context, the American Heart Association recommends that in cases of opioid overdose, a low dose of naloxone (ranging from 0.2 mg to 2 mg via *i.v.*, *i.o.*, or *i.m.*, or 2–4 mg *i.n.*) be administered, with repeat doses every 2–3 minutes if necessary. The dosing should be titrated to reverse respiratory depression and restore protective airway reflexes in order to minimize withdrawal symptoms. However, it is still not entirely clear whether the onset of this syndrome is a dose-dependent effect (Fairbairn et al. 2017; Lynn and Galinkin 2018; Lavonas et al. 2023).

In the context of fentanyl intoxications, the number of reports describing resistance to reversal with standard single doses of naloxone has increased in recent years (Schumann et al. 2008; Zuckerman et al. 2014; Fairbairn et al. 2017; Sutter et al. 2017; Bell et al. 2019). According to the National Emergency Medical Services Information System, the percentage of patients in whom a single naloxone dose is ineffective has risen proportionally with the growing abuse of potent opioids (Faul et al. 2017). In their study, Marco et al. (2018) observed opioid overdose patients in the emergency department from 2016 to 2017 and also noted an increase in the total dose of naloxone administered (with a median dose ranging from 4 to 8 mg) (Marco et al. 2018). The underlying causes of this issue are still being investigated. It is often assumed that the increased resistance is due to the high potency of fentanyl and its analogs and/or the extremely rapid onset of its toxicity and fatal outcomes (Lynn and Galinkin 2018; Comer and Cahill 2019). Because of this, the timeliness of antidote administration is critical (Green and Gilbert 2016). The need for a higher dose of naloxone may simply be due to the use of a high dose of fentanyl or a fentanyl analog that is resistant to naloxone (Lynn and Galinkin 2018). Additionally, the short half-life of naloxone presents a risk of re-narcotization and respiratory depression (Wong et al. 2017; Moss and Carlo 2019). Other researchers suggest that resistance to naloxone may be attributed to its mechanism of action. As a μ-opioid antagonist, naloxone reduces opioid-associated respiratory depression, but it is not effective in reversing fatal laryngospasm or rigidity of respiratory muscles, which are thought to be caused by interactions with receptors that do not belong to the opioid receptor family (Pergolizzi et al. 2021). Another hypothesis is that fentanyl and naloxone may share the same influx transporter in the brain. During opioid overdose, this transporter becomes saturated, preventing the antidote from crossing the BBB (Suzuki et al. 2010; Lynn and Galinkin 2018). While the exact mechanisms behind the reduced effectiveness of naloxone in fentanyl intoxications are still being clarified, Moss and Carlo (2019) propose an updated dosing range for the antidote, suggesting higher doses of 4–6 mg intramuscularly or an 8–12 mg *i.n.* equivalent. Considering the benefit-to-risk ratio, the authors suggest that this approach would be especially advantageous in scenarios involving self-administration of OTC antidote products or when emergency intervention by non-medical personnel is required (Moss and Carlo 2019).

One thing is clear from the data presented: the problem of managing fentanyl overdoses, its analogs, and newer synthetic opioids requires a rethinking not only of current naloxone dosing recommendations but also the exploration of new strategies for neutralizing opioid effects (Suzuki and El-Haddad 2016; Yeung et al. 2020). While the treatment of chronic opioid intoxication has solid foundations, the medical community is increasingly recognizing the need for more potent and long-acting antidotes in cases of acute poisoning (Yong et al. 2014; Volkow and Collins 2017; Baumann et al. 2018; Comer and Cahill 2019). In this regard, to date, the following potential alternatives to conventional antidotes are being investigated:

- ***Covalent nanoparticles containing naloxone*** – Polymer-based nanoparticles encapsulating naloxone serve for its sustained, linear (low and slow) delivery in the body. In this way, they may prove useful in reversing opioid overdose, reducing the need for repeated administration of the antidote. Additionally, they decrease the risk of acute opioid withdrawal or renarcotization, although these effects are highly dependent on the type of polymer and the precise formulation of the drug (France et al. 2021).
- ***Nalmefene*** **(*i.v., i.n.*)** – A higher affinity opioid antagonist that, depending on the route of administration, may exhibit a faster onset and longer duration of action than naloxone, reducing the likelihood of re-narcotization (Krieter et al. 2016; France et al. 2021).
- ***Methocinnamox*** – Methocinnamox is a novel μ-opioid receptor antagonist characterized by a prolonged duration of action. Unlike buprenorphine and methadone, it exhibits no agonistic activity at opioid receptors and is not anticipated to exacerbate the adverse effects of co-intoxication with alcohol or benzodiazepines. Methocinnamox markedly lowers the risk of renarcotization and inhibits the effects of subsequent opioid administration for at least one week. Furthermore, it holds promise as a prophylactic agent against opioid poisoning, particularly for law enforcement officers, first responders, and military personnel who may encounter accidental or intentional opioid exposure in the line of duty (Broadbear et al. 2000; Jordan et al. 2022).
- ***Serotonergic 5-HT$_{1A}$ receptor agonists*** – The neurotransmitter serotonin plays a crucial role in respiration, with 5-HT$_{1A}$ receptors having a key regulatory function in respiratory nuclei. It has been demonstrated that fentanyl and other opioid agonists block the activation of these receptors, which has spurred research into the potential for reversing respiratory depression through antagonism of 5-HT$_{1A}$ receptors (Martin et al. 1991). Several preclinical studies have shown promising results in this regard (Guenther et al. 2012; Ren et al. 2015; Fan et al. 2022; Song et al. 2025). According to France et al. (2021), this pharmacological class has several advantages, including its lack of impact on opioid receptors, which is particularly relevant in the context of the increasing prevalence of super opioids, as well as the potential to counteract a wider range of respiratory-depressing toxins, including those co-administered with opioids (France et al. 2021).
- ***Fentanyl-binding cyclodextrin scaffolds*** – *In vitro* studies suggest that due to their hydrophobic cavities, cyclodextrin oligosaccharides can serve as molecular „hosts“ for hydrophobic molecules such as fentanyl. The aim is to use them as a preventive measure against potential fentanyl and/or opioid intoxication, partic-

ularly for law enforcement agencies, first responders, and military personnel (Mayer et al. 2016). However, further *in vivo* studies are needed, especially those focusing on clarifying their toxicological potential.

- ***Detoxifying biomimetic ‚nanosponge' decoy receptors***– NarcoBond™ is a proteolipidic biomimetic „nanosponge" that mimics the lipid bilayer of cellular membranes. It directly captures opioids in the blood and lymph and indirectly from other tissues (*e.g.*, fat) through opioid diffusion into the plasma and subsequent sequestration in the nanosponge. At the same time, it does not cross the BBB and has a significantly longer half-life compared to naloxone (Federico et al. 2020). This represents a nonspecific approach, suitable for intoxication with various opioids, especially considering that the specific opioid involved is often unknown during treatment.
- ***Anti-opioid vaccines and antibodies*** – Vaccines and monoclonal antibodies may also serve as selective treatments for opioid overdose. These vaccines contain opioid-based haptens conjugated to larger immunogenic protein or particle carriers. They stimulate both innate and adaptive immunity to generate polyclonal antibodies that bind and sequester the target opioid in the serum, preventing it from crossing the BBB or interacting with naloxone or other opioids used in the treatment of chronic opioid dependence. The polyclonal antibodies induced by the vaccine thus prevent the distribution of the unbound and pharmacologically active drug to the brain, thereby reducing the risk of toxic effects (Martinez et al. 2023).
- Anti-opioid monoclonal antibodies (mAbs) exhibit *in vivo* properties comparable to those of polyclonal antibodies induced by vaccines. However, unlike vaccines, monoclonal antibodies provide almost immediate protection upon administration while minimizing concerns regarding individual variability, as mAbs do not rely on the patient's immune system characteristics (Baehr et al. 2022; Martinez et al. 2023).
- ***Intravenous lipid emulsions –*** There is growing interest and some evidence suggesting that intravenous lipid emulsions may be beneficial in certain cases of overdose with lipophilic substances. Although they do not act as opioid receptor antagonists, numerous studies indicate that they can be successfully used for detoxification through a mechanism known as „lipid sink" (Tampakis et al. 2020; Tikhomirov et al. 2022). However, this hypothesis remains an area of ongoing research, and further clinical studies are needed to definitively establish their safety and efficacy in this context.

Toxicological analysis of fentanyl in the management of overdoses

According to Boyer (2012), toxicology analysis of fentanyl in serum or urine is not critical but may aid in the emergency management of opioid overdose patients. Today, these analyses are more relevant to medical care during the recovery period and for monitoring compliance in chronic pain management (Armenian et al. 2018). The collected toxicological samples should include at least blood (preferably from the femoral vein), urine, and vitreous fluid, if available, along with additional samples if necessary. These samples must be appropriately preserved (Davis 2014).

Typically, hospital rapid tests are focused on the immunological detection of morphine and its metabolites (*e.g.*, heroin, codeine). Due to its structural similarity to morphine, such tests may also detect semi-synthetic opioids like oxycodone, hydromorphone, or hydrocodone, although with varying sensitivity. Since fentanyl is a fully synthetic opioid with no structural similarity to naturally occurring opiates, it does not cross-react with routine narcotic immunoassays. Therefore, without specific targeting, fentanyl is difficult to identify, and its detection in biological samples requires the use of specific screening tests aimed at it (Angelini et al. 2019). As a result, in the early 2010s, the development of automated immunoassays for fentanyl began, though very few are currently used in clinical laboratories (Wang et al. 2011).

According to Sutter et al. (2017), therapeutic concentrations of fentanyl range from 0.63 ng/mL to 2.0 ng/mL, whereas reported post-mortem serum concentrations of patients who died from fentanyl overdose range from 5 ng/mL to 120 ng/mL (mean = 36 ng/mL) (Sutter et al. 2017). To accurately determine serum concentrations in this range, highly sensitive methods such as gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-tandem mass spectrometry (LC-MS/MS) are required. Although these methods are more expensive and labor-intensive, the results hold greater medical and legal significance (Suzuki and El-Haddad 2016; Bergh et al. 2018). Furthermore, in response to the opioid crisis, there is an urgent need for enhanced surveillance to identify emerging opioids, along with standardization of analytical methods and requirements for data sharing at the local, state, and national levels (Morrow et al. 2018).

Combatting the abuse of fentanyl: Strategies and solutions

The opioid crisis necessitates multidimensional solutions targeting each stage in the progression toward opioid addiction. Frank and Pollack (2017) distinguish between "use reduction" and "harm reduction" as strategic objectives for authorities aiming to minimize the social harm associated with fentanyl use. The former seeks to reduce the volume of illicit drug consumption, while harm reduction aims to mitigate the adverse outcomes associated with such use, regardless of overall consumption levels (Frank and Pollack 2017). Specifically, use reduction focuses on decreasing the distribution, sale, and possession of drugs through measures such as criminal penalties and law enforcement. Although dismantling illicit labs and other points along the fentanyl supply chain is critical for disrupting the illegal market, evidence indicates that enforcement efforts alone are insufficient and often result in severe unintended public health consequences (Socías and Wood 2017). Beyond escalating violence in drug markets, evidence indicates that a focus on law enforcement often drives the illicit production of newer, more potent, and more toxic drugs (Beletsky et al. 2020). Empirical evidence suggests that the current opioid crisis is a predictable consequence of reducing the supply of opioid analgesics and heroin without addressing the needs of those already dependent on them (Socías and Wood 2017).

Socías and Wood (2017) frame the harms associated with fentanyl abuse as a public health crisis rather than a criminal or moral issue. In this context, harm reduction involves both treating individuals affected by opioid dependency and encouraging safer drug use practices. Primarily, this requires public awareness regarding the prevalence of counterfeit pills or adulterated substances containing high concentrations of fentanyl (Krieger et al. 2018; Reed et al. 2022). Some authors recommend beginning with a small test dose to evaluate potency before proceeding with higher doses. Additionally, fentanyl test strips are promoted among users, aiding in the identification of fentanyl presence within substances. Patients should also be advised against using drugs alone, ensuring that someone is available to intervene or call for medical assistance if necessary. Ideally, drug use should occur in settings with outward-opening doors and emergency alert systems (Harm Reduction Coalition 2001; Walley 2015). The latest American Heart Association guidelines (2023) recommend that both users and their families be trained to recognize overdose symptoms. Given the scale of the issue, widespread community training in cardiopulmonary resuscitation (CPR) and the use of OTC naloxone products (where accessible) is increasingly important (Lavonas et al. 2023). Regarding naloxone, user-friendly formulations such as *i.n.* sprays and auto-injectors – designed for higher-dose delivery – are recommended (Frank and Pollack 2017).

In certain countries, special rooms or facilities for injection and consumption have been introduced, where individuals with dependency can use illicit drugs under medical supervision. This unconventional approach is recognized as an effective intervention, with evidence showing that it promotes safer injection practices, improves access to primary care, reduces HIV and hepatitis C transmission, and decreases overdose rates (Tran et al. 2021; Parkes et al. 2022; Shorter et al. 2023). As of July 2016, controlled injection or consumption facilities were prohibited in the United States, though they were common in Canada and various European nations (e.g., Spain, Denmark, the Netherlands, Norway, Switzerland, and Germany) (Pfeiffer 2016; Frank and Pollack 2017).

Clinicians, law enforcement personnel, and first responders should also be trained to recognize potential fentanyl exposure risks. They must exercise extreme caution to avoid accidental exposure, whether via skin contact, inhalation of airborne powder, or inadvertently transferring materials from hands to mucous membranes. Fentanyl-contaminated paraphernalia, patches, and other items may still contain enough fentanyl to cause overdose and should be disposed of safely. Gloves should be worn at all times when handling materials, and if exposed to loose powder, responders should use a face mask or contact hazardous materials services (Adams et al. 2023).

Conclusion

The distinct pharmacological profile of fentanyl, a potent μ-opioid agonist, underpins both its widespread clinical use in analgesia and anesthesia and its central role in the evolving crisis of synthetic opioid misuse. Fentanyl overdose poses a complex and often fatal challenge, characterized by the rapid onset of respiratory depression and unique complications such as wooden chest syndrome, a condition marked by severe chest wall rigidity. While naloxone remains the primary antidote, emerging evidence indicates that higher doses may be necessary and that it may be less effective in reversing non-respiratory effects, such as chest wall rigidity. These limitations underscore the urgent need for further research into more effective and longer-acting countermeasures to mitigate fentanyl's risks in both clinical and security contexts. Addressing this public health crisis demands a balanced and sustained approach that integrates strategies for both misuse prevention and harm reduction.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Author contributions

Conceptualization, S.S.G.; methodology, S.S.G; software, S.S.G.; formal analysis, S.S.; investigation, S.S.G., M.R-I., N.K.; resources, S.S.G., S. D. G. K., S. D. and M. P.; data curation, S.S.G.; writing original draft preparation, S.S.G. and M. P.; writing – review and editing, S.S.G. and S. Z.; visualization, S.S.G.; supervision, P. M.; project administration, S.S.G.; funding acquisition, P.M. All authors have read and agreed to the published version of the manuscript.

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Data availability

All of the data that support the findings of this study are available in the main text.

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