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REVIEW

New Synthetic Opioids: Clinical Considerations and Dangers

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ABSTRACT

Since the early 2010s, synthetic opioids have significantly contributed to overall opioid-related overdose mortalities. For point of reference, of the 68,630 opioid-related deaths recorded in 2020, 56,516 involved synthetic opioids. During much of this period, fentanyl has been the most commonly used synthetic opioid. This time when fentanyl was the most popular opioid has been called the "third wave" of the opioid crisis, partly because it led to a sharp rise in deaths from overdoses. Other synthetic opioids, such as carfentanil, protonitazene, and isotonitazene, have also become more widely diverted for nonmedical used. Carfentanil is an even more potent fentanyl derivative that was initially used in the mid-1980s as a general anesthetic for large animals such as elephants. Related to its strong affinity for mu opioid receptors, carfentanil is still utilized in medicine and science today as a radiotracer for positron emission tomography imaging. Protonitazene and isotonitazene

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belong to a novel class of synthetic opioids called benzimidazoles that were manufactured in the 1950s as novel analgesics. These agents have come under recent scrutiny as designer synthetic opioids becoming more prevalent. However, to date, there is incomplete data regarding the prevalence of synthetic opioids, as traditional toxicology screenings may not be sensitive to detect these compounds at such low doses post-mortem, particularly when blood is drawn from the periphery instead of central tissues such as the brain, lung, or heart. This narrative review aims to highlight the clinical challenges presented by these new synthetic opioids.

Keywords: Synthetic opioids; Fentanyl; Carfentanil; Protonitazene; isotonitazene; Overdose

Key Summary Points

Carfentanil, protonitazene, and isotonitazene are three new synthetic opioids that negatively contribute to the opioid pandemic. The potency and effectiveness of these synthetic opioids significantly enhance the risk of overdose and have increased mortality

These readily available, inexpensive fentanyl analogs have permeated the drug market. According to the case studies, a pattern of drug users with substance use disorders dying from overdoses after ingesting narcotics laced with carfentanil has arisen

The OUD treatment recommendations that are now in place present additional difficulties. The dose of naloxone advised does not seem to be sufficient to reverse the effects of the synthetic opioids

To deal with these more potent synthetic opioids, the recommended naloxone dosage and course of therapy must be modified. To find effective alternative reversal treatments for overdoses and alternative pain-relieving formulas/medications, advanced and accelerated pharmaceutical research is essential

As time goes on, the opioid issue will require cooperation from the medical community, policymakers, and law enforcement. To effectively treat OUD, lessen addiction, and stop further substance use, a variety of entities, agencies, and procedures can all be put into place simultaneously, from education about OUD treatment and proper guidelines to pharmacological developments

Additionally, educating the public on the risks posed by the new synthetic opioids, particularly for those at risk, and offering assistance to those in need may help lower the incidence of fatal overdoses

INTRODUCTION

An opioid crisis in the US began in the 1990s when prescription opioid use accelerated, followed by a second wave in 2010 related to heroin use [1]. In 2013, the popularity of illicit synthetic opioid use, such as fentanyl, led to the third wave of the crisis, causing a marked increase in fatal overdoses [1]. Synthetic opioid use is nearly twice as likely to lead to an overdose death compared with prescription opioids or heroin [1, 2]. The low production cost and high potency of fentanyl make it an attractive substance to mix with heroin and other illicit drugs [3]. Since its introduction, fentanyl and its analogs have infiltrated the US heroin supply. They are found in pills that look like commonly known opioids or benzodiazepines and are known as “pressed pills” [4].

Fentanyl and its analogs cause severe central nervous system (CNS) and respiratory depression, which may lead to death, especially in an unsuspecting, opioid-naive person [4]. Fentanyl analogs are emerging at an alarming rate, and their detection can be difficult since they often have novel chemical structures [4]. Another challenge is found in internet distribution, which makes these drugs more attainable and can cause confusion between pharmaceutically and illicitly manufactured opioids [5]. To combat these growing challenges, clinicians should recognize the hallmark signs of opioid toxicity, such as respiratory distress, altered mental status, and miosis [4]. Concerning emergency overdose treatment, a larger dose of naloxone is required to reverse the effects of high-potency opioids compared with heroin, up to the point that repeated doses or a naloxone may be needed to control respiratory depression [4]. This is related to the fact that fentanyl is very potent, allowing it to outcompete naloxone for the mu opioid receptor (MOR). Further, because it is very lipophilic, it will stay in the body longer than other opioids. This narrative review, therefore, aims to highlight the clinical challenges presented by these new synthetic opioids.

COMPLIANCE WITH ETHICAL GUIDELINES

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. This was a narrative review. The sources for this review are as follows: searching on PubMed, Google Scholar, Medline, and ScienceDirect from 1990 to 2022 using combinations of the keywords: synthetic opioids, fentanyl, carfentanil, protonitazene, isotonitazene, overdose. We attempted to include as many primary sources as possible.

DANGERS OF SYNTHETIC OPIOIDS

Since the early 2010s, synthetic opioids have significantly contributed to overall opioid-related overdose mortalities. For reference, of the 68,630 opioid-related deaths recorded in 2020, 56,516 involved synthetic opioids (primarily fentanyl and its analogs) [6, 7]. This rise in synthetic-opioid related use in recent years has been accompanied by a corresponding, decrease in the use of other illicit opioids such as heroin [8]. Some potential reasons why synthetic opioid use has become so ubiquitous have been postulated to include lower production costs, stronger or longer lasting highs, and increasingly efficient synthesis by manufacturers [8, 9]. As noted by the US Drug Enforcement Agency, a relatively common factor in synthetic opioid overdoses is their utilization as cheap adulterants in preparations of other illicit drugs [10]. This is not to say that there are not users who intentionally seek out synthetic opioids. Still, the role of synthetic opioids as additives unknown to the user is nevertheless thought to play a significant role. Fentanyl and other synthetic opioids have been detected as components in mixtures of cocaine, methamphetamine, heroin, and counterfeit pills [11]. The increased danger of overdose from synthetic opioids versus substances such as heroin is simply related to their greatly increased potency and efficacy, as well as increased availability in the drug supply [12]. What may be a "typical" dose of an opioid like heroin is certainly lethal without rapid intervention when a synthetic opioid like fentanyl or carfentanil is substituted in its place. Furthermore, heroin overdose can take 20–30 min before it leads to a fatality. Fentanyl, on the other hand, can precipitate a profoundly dangerous and life threatening respiratory arrest within 2–5 min [12].

Presentation

The signs and symptoms of overdose from synthetic opioids are essentially the same as those seen from overdose secondary to natural and semisynthetic opioids. Through various pharmacological mechanisms, synthetic opioids potently act on the CNS to produce various effects, ranging from euphoria and analgesia to respiratory depression, coma, and death [12].

Respiratory arrest followed by death is the most serious outcome of an overdose. However, even nonfatal overdoses can produce variably debilitating results, with life-altering effects such as permanent parkinsonism or psychosis secondary to hypoxic brain injury [12]. The treatment of opioid overdose revolves chiefly around restoring a patient's ability to spontaneously breath. As is standard in treating opioid overdoses in general, the MOR antagonist naloxone is the first-line medication for reversal in the case of synthetic opioid overdose. Given the increased potency of synthetic opioids, it has been hypothesized that increased dosages of naloxone are necessary to reverse their effects [11, 13]. Additionally, given the wide therapeutic window of naloxone, and with the increasing prevalence of these substances in circulation, suggestions have been made to simply increase the standard doses of naloxone administered by the first responders who initially arrive on scene to an opioid overdose [12].

NEW SYNTHETIC OPIOIDS OVERVIEW

Carfentanil

Carfentanil is an extremely potent fentanyl-derivative initially circulated in the mid-1980s as a general anesthetic for large animals such as elephants. Currently, carfentanil still sees medical and scientific use as a radiotracer for positron emission tomography imaging, related to its high affinity for MORs in brain tissue [14]. Outside of its legitimate clinical uses, carfentanil is commonly known by street-names such as "drop dead" and "elephant tranquilizer". It has been commonly found as an additive in other illicit drugs such as heroin and cocaine, meaning many unwitting users may be completely unaware of its presence [15]. As carfentanil is not regularly tested for in most routine drug screening panels, investigators are still unsure of the extent to which it contributes to yearly opioid overdose deaths. It is suspected, however, that it plays a significant role. For instance, one recent report demonstrated that a large spike and fall of opioid-related overdose deaths between 2016 and 2017 correlated with the amounts of carfentanil seized by the authorities [16].

As a fentanyl derivative, carfentanil produces effects similar to other opioids, including analgesia, euphoria, bradycardia, respiratory depression, hypotension, loss of consciousness, and death. What sets carfentanil apart from most other opioids is its extremely high potency. For instance, it is over 1000 times more potent than morphine at the MOR, and its affinity for the MOR is 50 times greater than fentanyl [17]. Given the implication of MOR in respiratory depression, the high potency of carfentanil means that even very small doses can produce extremely rapid detrimental effects. Carfentanil may be found in pill, powder, and liquid forms [15]. As is common practice in reversing overdose due to other opioids, the accepted method for treating carfentanil overdose relies on the pure MOR antagonist naloxone. Recent clinical studies have suggested that higher doses of naloxone may be necessary to reverse carfentanil's effects. However, further analysis is needed to confirm this with certainty [17, 18].

Protonitazene

Protonitazene belongs to a novel class of synthetic opioids that was initially manufactured in the 1950s as a potential alternative opioid for medical use [19]. Related to observed adverse effects in early clinical trials, its study for medical use was discontinued. For the majority of the time since its original manufacture in the mid-twentieth century, protonitazene remained rather obscure. This ceased to be the case between 2019 and 2021, when protonitazene was found in forensic analysis in cases seen in the USA, Canada, Europe, and Australia [19, 20]. As its appearance as an illicit drug remains relatively recent, protonitazene remains unregulated in the European Union at the time of this present writing. The USA has now classified protonitazene as a Schedule I substance [19]. Manufacture has been linked to various companies in China that offer shipping to other countries via online sales.

As a member of the novel opioid subclass of benzimidazoles, protonitazene behaves as a strong MOR agonist with a high potentiality for addiction [21]. Analyses of protonitazene have demonstrated that at the MOR, it possesses an efficacy of approximately 1.07–1.29 times greater than that of fentanyl, and its potency is much greater than morphine [19]. Other opioids share common effects: analgesia, euphoria, respiratory depression, coma, and potentially death [21, 22]. Protonitazene appears to be primarily manufactured for illicit use in tablet and powder forms, though it has also been found in liquid form [19, 22]. As with other synthetic opioids, there is serious potential for protonitazene to be used as an additive in other illicit drugs, leading to unwitting overdose by the user [22]. As a recent Australian study noted, the effects of synthetic opioids such as protonitazene can be highly unpredictable, leading to a high risk of accidental overdose in even experienced users [20]. In the case of overdose, naloxone has been shown to successfully reverse protonitazene in a clinical setting [20].

Isotonitazene

Like protonitazene, isotonitazene also belongs to the novel benzimidazole class of opioids. It was also initially synthesized in the 1950s [23]. This drug never saw any medical use and remained in relative obscurity until being identified by authorities in Midwestern USA in 2019 [24]. Reports of isotonitazene use in the USA are still fairly uncommon at present. However, in mid-2020, the USA classified isotonitazene as a Schedule I substance [25]. Like protonitazene, the primary source of isotonitazene is China, where manufacturers synthesize the product and market it overseas [24].

As with the other substances in this study, many of the primary effects of isotonitazene are mediated through MOR agonism. Isotonitazene's potency is comparable to fentanyl, which may be found in pill, powder, and liquid forms [25]. As expected, the effects of isotonitazene range from euphoria and analgesia to respiratory depression, coma, and death [23]. As with other synthetic opioids, much of the isotonitazene sold on the streets is not marketed as isotonitazene. The Drug Enforcement Agency (DEA) has reported that most of the isotonitazene that has been analyzed in the USA so far was utilized as a cheap filler for other illicit substances such as heroin, or sold as counterfeit versions of opioids such as hydromorphone [24]. At present, there is still limited data regarding how often isotonitazene is implicated in drug overdoses. Given the lack of data, there have yet to be any studies addressing the recommended dosage of naloxone needed to reverse isotonitazene overdose. It is suspected, however, that a higher dose than that usually employed for opioid overdose may be required [25]. Table 1 lists the synthetic opioids reviewed in this section and their strengths relative to both fentanyl and morphine.

TREATMENT CHALLENGES WITH FENTANYL AND OTHER SYNTHETIC OPIOIDS

The rise of fentanyl and its analogs have brought many challenges to treating opioid use disorder (OUD) [26]. One of which is that fentanyl's pharmacologic profile has a higher potential of addiction and overdose deaths compared with morphine and heroin [27]. Fentanyl is a full-efficacy MOR agonist that is 50 to several 100 times more potent than morphine, depending on the route of administration [27]. Fentanyl's lipophilicity allows for rapid plasma distribution and the ability to cross the blood–brain barrier. This is one of the features responsible for fentanyl's faster onset,

Table 1 Synthetic opioids and their strengths relative to both fentanyl and morphine

Fentanyl analog	Strength in terms of fentanyl	Strength in terms of morphine
Carfentanil	50× greater	1000× greater
Protonitazene	1.07–1.29× greater	130× greater
Isotonitazene	Roughly equal	2.5 × greater

shorter analgesic duration, and higher analgesic potency compared with morphine [28]. As stated earlier, along with the potency of fentanyl, it also contributes to why higher amounts of naloxone may be needed to reverse a fentanyl-related overdose.

Another challenge at hand is that the current OUD treatment guidelines were created for morphine and heroin, which have a much lower potency compared with the new synthetic opioids [29]. Fentanyl users are at a greater risk of precipitated withdrawal by buprenorphine when treatment is initiated [30, 31]. The withdrawal mechanism may be due to fentanyl's lipophilicity, which causes prolonged and varied renal clearance, or due to MOR desensitization/availability [30]. Current methadone treatment protocols are conservative, and the dosing regimen does not reach a therapeutic dose quickly enough, causing a lack of perceived efficacy in patients [29]. Through ongoing research, it is pertinent that optimal treatment strategies and dosing for fentanyl-related OUD are created regarding buprenorphine, methadone, and naloxone [28]. The addition of short-acting opioids in treating patients with acute pain and withdrawal symptoms can be a helpful tool [26]. Unfortunately, many physicians fear exacerbating addiction or lack training to treat OUD with short-acting opioids [26]. In addition to research, policies and regulations need to be implemented and physician education on proper treatment of synthetic OUD so that patients fighting OUD can receive proper and adequate treatment moving forward [32].

Treatment challenges exist within the education and administration of pain management medications [26]. With fentanyl and fentanyl analogs being on the rise and the tenfold increase in mortality within the first 4 weeks after discontinuation of methadone treatment, follow-up and aftercare need adaptation and improvement [29]. Hospital protocols, clinician training in addiction, and legal restrictions have perpetuated ongoing challenges to successfully and effectively manage pain and limit addiction and overdose [26]. Challenges further exist with discharge planning and compliance with sufficient post-discharge and follow-up treatments [26]. Application and integration of ongoing research and evidence-based treatment, as well as protocols and the integration and collaboration of addiction consultants for inpatient clinicians may also overcome the preceding challenges [26]. With all this in mind, it is time to turn to clinical cases involving these synthetic opioids.

CLINICAL CASES

Clinical Considerations for Detection of New Synthetic Opioids

Selected Case Reports

The selected case reports below detail the unique challenges with detection, management, and clinical presentation of acute intoxication with various synthetic opioids. All blood analyses, toxicology screenings, autopsy reports, and certified cause of death were included wherever available. Additional history and laboratory testing of drug paraphernalia were included wherever applicable. Table 2 contains the pertinent history, toxicology findings, and cause of death from these selected cases, as well as additional cases of confirmed synthetic opioid intoxication.

Case 1: Acute carfentanil intoxication [33].

A 38-year-old male with a known history of heroin use was found deceased in his bathroom surrounded by drug paraphernalia. Analysis of the femoral blood showed carfentanil (221 ng/L) without evidence of any other drugs, although urine screening was positive for morphine, codeine, hydromorphone, and norfentanyl. Autopsy showed pulmonary congestion and cardiomegaly. Toxicology results and autopsy findings indicated carfentanil drug toxicity as the cause of death [33].

Case 2: Acute protonitazene intoxication [34].

A 41-year-old male with a known history of substance use was found deceased in his hotel room after illicit drug use with his girlfriend. They had received drugs from an unknown source that they believed to be cocaine. After consuming these illicit drugs, she left the hotel room to go to the vending machine, but upon

returning to the hotel room she found him lying on the bed with his fists clenching his chest holding his cell phone. Investigators also found an unspecified pill on the side table next to the bed. Analysis of cardiac blood was positive for protonitazene (1400 ng/mL), etodesnitazene (1.8 ng/mL), cocaine (1500 ng/mL), benzoylecgonine (3100 ng/mL), cocaethylene (260 ng/mL), delta-8 tetrahydrocannabinol (THC)(9.0 ng/mL), delta-9 tetrahydrocannabinol (THCC) (6.8 ng/mL), doxepin (110 ng/mL), and ethanol (47 mg/dL). Autopsy findings were unavailable, but the cause of death was listed as mixed drug toxicity [34].

Case 3: Acute isotonitazene intoxication and withdrawal [35].

A man with a known history of smoking isotonitazene was found deceased in his home. He had voluntarily admitted himself for isotonitazene detoxification 2 months prior. During that hospitalization, he described how he had developed an addiction to the relaxant and euphoric effects of isotonitazene that quickly lead to a physical dependence requiring greater and greater doses to avoid withdrawal. He explained that his previous withdrawal symptoms often included sweating, nausea, jaw tension, and intense psychic stress. While detoxing in the hospital, he exhibited psychomotor agitation, insomnia, and episodes of cold sweats consistent with opioid withdrawal. The patient was discharged after only 7 days at his request following the cessation of withdrawal symptoms. Providers in the hospital conducted a psychoeducational interview and determined that his judgment was intact with the absence of cravings; therefore, he was allowed to leave [35].

Upon discovering his body 2 months later, investigators found a vaporization pipe and a white powdery substance later confirmed to be isotonitazene. Autopsy findings revealed gastric material in the upper and lower respiratory tract. Analysis of his hair confirmed isotonitazene use in the month between his discharge and subsequent death. Femoral blood analysis was positive for isotonitazene (0.59 ng/mL), lorazepam (12 ng/mL), THC (56 ng/mL), 11-hydroxy-THC (1.8 ng/mL), carboxy-THC (6.5 ng/mL), and cannabinol (CBN) (2.9 ng/mL). The higher concentrations of isotonitazene distributed throughout the body compared with the femoral blood and his significant history were highly suggestive of isotonitazene intoxication leading to his death [35].

Case 4: Positive central blood screening with confirmed synthetic opioids at the scene [33].

A 38-year-old male with a known history of alcoholism was found deceased on the floor of his friend's bathroom. His family denies any history of illicit drug use, but drug paraphernalia including a syringe, spoon, and powdery substance was found at the scene. Analysis of the powdery substance identified a mixture of heroin, fentanyl, and carfentanil. No formal autopsy was conducted but given the presence of opioids and track marks on the decedent's arms, further toxicology analysis was performed. Initial urine screening was positive for morphine, hydromorphone, fentanyl, and norfentanyl, but there was no evidence of carfentanil. Carfentanil (30.1 ng/L) was only identified after analysis of the subclavian blood [33].

Case 5: Negative peripheral blood screening despite a history suggestive of opioid use [36].

A 34-year-old male with a history of tobacco, alcohol, marijuana, and heroin use was found deceased in his van. Various drug paraphernalia including a syringe, spoon, and yellow baggy with a brown substance was found in the van. Analysis of the spoon identified caffeine, carfentanil, diphenhydramine, fentanyl, para-fluoroisobutyryl fentanyl, furanyl fentanyl, heroin, hydromorphone, mannitol, 6-monoacetylmorphine, morphine, noscapine, and quinine. Initial peripheral blood testing was negative, but given the presence of synthetic opioids identified on the drug paraphernalia additional cardiac blood screening was performed. Heart blood was positive for carfentanil (1.3 ng/mL), furanyl fentanyl (0.34 ng/mL), morphine (< 20 ng/mL), and hydromorphone (< 20 ng/mL). Additional urine screening was positive for morphine, hydromorphone, 6-monoacetylmorphine, and hydrocodone. Autopsy findings include mild hypertensive heart disease with left ventricular hypertrophy and mild hepatic steatosis. Given the history and positive cardiac blood toxicology, cause of

death was listed as mixed drug intoxication [36].

Case 6: Targeted screening for low-dose synthetic opioid [36].

A 25-year-old male with a history of tobacco, alcohol, marijuana, spice, and prescription pain medication use was found face down on a mattress in a tent where he had been living with his mother. Before his death, he complained of "itching all over" and his sister described him as sounding "very intoxicated." Initial peripheral blood screening was positive for benzoylecgonine (460 ng/mL). His urine screening was highly suggestive of carfentanil, but these results were inconclusive due to the relatively low dose. Given his symptoms of "itching all over" and inconclusive urine results, cardiac blood was tested specifically for the presence of carfentanil, which was ultimately positive at very low quantities (0.12 ng/mL). Additional testing of vitreous humor showed cocaine (40 ng/mL) and benzoylecgonine (510 ng/mL), but no evidence of carfentanil. Autopsy showed mild left ventricular hypertrophy. Ultimately, given the significant history and positive cardiac blood toxicology, cause of death was determined as carfentanil intoxication [36].

Case 7: Illicit drug contamination with synthetic opioids [34].

A 43-year-old male presented to the hospital after ingesting what he believed to be a "30-mg Percocet" tablet. His urine toxicology screening was positive for benzodiazepines and marijuana, but no evidence of opioids. He was treated for an accidental overdose but eventually discharged from the hospital 5 h later before being found deceased. Postmortem femoral blood analysis was positive for isotonitazene (0.71 ng/mL), brorphine (3.6 ng/mL), THC (6.7 ng/mL), and diphenhydramine (530 ng/mL). His certified cause of death was listed as mixed drug toxicity [34].

Case 8: Illicit drug contamination with synthetic opioids [37].

A 43-year-old male with a known history of opioid dependency presented to the emergency department (ED) with acute opioid overdose. He was prescribed buprenorphine as an opioid substitute but admitted to relapsing with heroin and crack cocaine approximately once per month. Before presenting at the ED, he smoked his normal amount of "heroin" before feeling excessively dizzy after only a few inhalations. Nearby witnesses saw him collapse and quickly administered 2 mg of intramuscular naloxone and he quickly regained consciousness with a Glasgow Coma Score (GCS) of 15/15. Vitals signs and electrocardiogram (ECG) in the ED were significant for hypertension but otherwise unremarkable. His blood work showed evidence of acute kidney injury and the presence of isotonitazene (0.18 ng/mL), cocaine, cocaine metabolites, buprenorphine, and buprenorphine metabolites. He was kept overnight for observation and intravenous (IV) fluids and ultimately released the following day when his kidney function had normalized [37].

Case 9: Ineffective dose of Narcan with synthetic opioids [33].

A 33-year-old female with a recent overdose 1 week prior was found deceased in her bathroom surrounded by drug paraphernalia. A naloxone dose was found in the bathroom and a single dose had been administered. Postmortem analysis of iliac blood was positive for carfentanil (145 ng/L), morphine (10.9 μg/L), THC (2.7 μg/L), and 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (29.0 μg/L). Urine was positive for 11-nor-9-carboxy-delta-9-tetrahydrocannabinol, morphine, and codeine. No autopsy findings were available, but the cause of death was listed as mixed drug intoxication [33].

Case 10: Extended bioavailability of synthetic opioids leading to re-intoxication following naloxone administration [37].

A 41-year-old male with a history of crack cocaine and cannabis use was found unresponsive on the steps of his apartment. Of note, the patient had a history of intentional overdose with prescription medications in the setting of depression a few years prior. At the time of his death, he was prescribed sertraline to manage his depression. Upon arrival, emergency services noted significant respiratory depression and began cardiopulmonary resuscitation (CPR). They administered two doses of 400 μg naloxone intravenously after which he regained consciousness. Following administration of naloxone, his GCS was 14/15. Upon arrival at

the hospital, his GCS slightly decreased to 13/15. Given his apparent respiratory difficulties, chest x-ray and polymerase chain reaction (PCR) testing were performed to rule out possible COVID-19 infection. During his hospital stay, the patient admitted to smoking a new "resin," which he believed to be cannabis, but denied any history of IV drug or heroin drug use. Forty-six minutes following his previous naloxone dose, he again showed signs of respiratory distress and required an additional four doses of 200 μg IV naloxone for a total dose of 800 μg. His symptoms improved temporarily, but 2 h later, he showed signs of respiratory depression. Ultimately, he was started on a continuous infusion of IV naloxone at a rate of 480 μg/h for 12 h. Upon completing this infusion, he showed no additional signs of respiratory changes and was ultimately discharged 21 h after his initial presentation. His toxicology report at the time of admission was positive for cocaine, buprenorphine metabolites, and isotonitazene (0.81 ng/mL) [37].

Case 11: Prolonged bioavailability of synthetic opioids [33].

A 28-year-old male with a history of heroin use was found deceased in his jail bed. History suggested heroin use the previous night. Subsequent blood analysis from the iliac was positive for carfentanil (23.3 ng/L) and 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (9.6 μg/L). Autopsy revealed pulmonary edema and cause of death was acute carfentanil intoxication [33]. Table 2 summarizes the cases spoken of in this section and additional cases seen in the literature.

Traditional toxicology screenings may not have the necessary sensitivity to detect these compounds at such low doses post-mortem, particularly when blood is drawn from the periphery instead of central tissues such as the brain, lung, or heart [33, 35, 36, 39]. Additional analysis and specific testing may be required when the history, clinical presentation, or other factors suggest opioid intoxication [35, 36]. In addition to high-sensitivity testing, laboratories need to work closely with law enforcement and public health officials to remain current on regional and temporal shifts in recreational drug use to ensure proper screening as new synthetic opioids continue to emerge in the local drug supply [34, 40].

Naloxone is an effective treatment against lethal doses of carfentanil in animal models. Yet there has been some evidence to suggest that a much higher dose of naloxone is required due to the relative potency and extended bioavailability of synthetic opioids [33, 37, 41–43]. Patients with suspected synthetic opioid intoxication should be closely monitored following administration of naloxone given the increased risk of re-intoxication due to the extended bioavailability outlasting the antagonist effects of naloxone [37].

CONCLUSIONS

New synthetic opioids, carfentanil, protonitazene, and isotonitazene, play a detrimental role in the opioid epidemic. The potency and efficacy of these synthetic opioids increase the overdose potential substantially and have raised fatalities. These consequences and outcomes are a dire matter, especially to unsuspecting users. The addition of these cheap and easily attainable fentanyl analogs has infiltrated the drug market. As seen in these case studies, a pattern of individuals with substance use disorder using drugs laced with carfentanil leading to overdose deaths has emerged. Additional challenges include the current treatment guidelines regarding OUD. The recommended dose of naloxone does not appear to be effective enough at reversing the effects of the synthetic opioids. As seen in the case studies, treatment attempts with naloxone were unsuccessful. Substantial evidence determines a need in treatment research to battle this evolving crisis. The appropriate dosage of naloxone and continued treatment guidelines must be updated to handle these stronger synthetic opioids. Advanced and expedited pharmaceutical research is of utmost need to identify effective alternative reversal remedies for overdosages and alternative pain-reducing formulas/medications [44–46].

As we move forward, it will take collaboration from medical professionals, policy makers, and law enforcement to battle the opioid crisis.

Table 2 Clinical cases involving synthetic opioids

Case	Pertinent history	Blood source	Synthetic opioid found	Additional findings	Cause of death
1. Shanks et al., 2017	38 y/o M with a history of heroin use was found in his bathroom surrounded by drug paraphernalia [33]	Femoral blood	Carfentanil (221 ng/L)	Morphine (urine) Codeine (urine), hydromorphone (urine) Norfentanyl (urine)	Carfentanil drug toxicity
2. Papsun et al., 2022	41 y/o M with a known history of substance use was found deceased in his hotel room after suspect cocaine use. He was found with his fists clenching his chest holding his cell phone [34]	Cardiac blood	Protonitazene (1400 ng/mL), etodesnitazene (1.8 ng/mL)	Cocaine (1500 ng/mL) Benzoylecgonine (3100 ng/mL) Cocaethylene (260 ng/mL) THC (9.0 ng/mL) THCC (6.8 ng/mL) Doxepin (110 ng/mL Ethanol (47 mg/dL)	Mixed drug toxicity
3. Mueller et al., 2021	M with a known history is isotonitazene use was found deceased 2 months after in-patient detox. A vaporization pipe and white powdery substance at the scene tested positive for isotonitazene. Autopsy findings showed blood congestion of the organs, presence of gastric material in the upper and lower respiratory tract, and lung edema [38]	Femoral blood	Isotonitazene (0.59 ng/mL)	Lorazepam (12 ng/mL) THC (56 ng/mL) Hydroxy-THC-OH (1.8 ng/mL) Carboxy-THC (6.5 ng/mL) CBN (2.9 ng/mL)	Isotonitazene intoxication

Table 2 continued

Case	Pertinent history	Blood source	Synthetic opioid found	Additional findings	Cause of death
4. Shanks et al., 2017	38 y/o M with a history of alcoholism was found unresponsive in a friend's bathroom. There was a syringe, spoon, and powdery substance later identified as heroin, fentanyl, and carfentanil [33]	Subclavian blood	Carfentanil (30.1 ng/L)	Morphine (urine), hydromorphone (urine) Fentanyl (urine) Norfentanyl (urine)	Acute carfentanil intoxication
5. Swanson et al., 2017	34 y/o M with a history of tobacco, alcohol, marijuana, and heroin use was found deceased in his van. Various drug paraphernalia including a syringe, spoon, and yellow baggy with a brown substance were found in the van. Autopsy showed mild hypertensive heart disease with left ventricular hypertrophy and mild hepatic steatosis [36]	Heart blood	Carfentanil (1.3 ng/mL)	Furanyl fentanyl (0.34 ng/mL) Morphine (< 20 ng/mL) Hydromorphone (< 20 ng/mL)	Mixed drug intoxication
6. Swanson et al., 2017	25 y/o M with a history of tobacco, alcohol, marijuana, spice, and prescription pain medication use was found face down on his mattress. He complained of "itching all over" and his sister describe him as sounding "very intoxicated" before his death [36]	Heart blood	Carfentanil (0.12 ng/mL)	Benzoylecgonine (460 ng/mL) (peripheral blood)	Carfentanil intoxication
7. Papsun et al., 2022	43 y/o M presented with accidental overdose after taking what he thought was '30-mg Percocet." Urine toxicology in the ED showed benzos and marijuana [34]	Femoral blood	Isotonitazene (0.71 ng/mL) Brorphine 3.6 (ng/mL)	THC (6.7 ng/mL) Diphenhydramine (530 ng/mL)	Combined drug toxicity

Table 2 continued

Case	Pertinent history	Blood source	Synthetic opioid found	Additional findings	Cause of death
8. De Baerdemaeker et al., 2022	43 y/o M with a history of opioid dependency presented to the ED with acute opioid overdose. He was prescribed buprenorphine as an opioid substitute but admitted to relapsing with heroin and crack cocaine. Before presentation at the ED, he smoked his normal amount of "heroin" before losing consciousness. He was able to regain consciousness following 2 mg dose of intramuscular (IM) naloxone. He remained in the hospital overnight for monitoring of possible acute kidney injury (AKI) [37]	Peripheral blood	Isotonitazene (0.18 ng/mL)	Cocaine Cocaine metabolites Buprenorphine, buprenorphine metabolites	N/A
9. Shanks, et al., 2017	33 y/o F with recent overdose 1 week prior was found deceased on her bathroom floor. There was drug paraphernalia and Narcan kit with a single dose missing found in the bathroom [33]	Iliac blood	Carfentanil (145 ng/L)	Morphine (10.9 µg/L) THC (2.7 µg/L) 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (29.0 µg/L)	Mixed drug intoxication
10. Shanks et al., 2017	41 y/o M with a history of cannabis and crack cocaine use was found unresponsive. Before losing consciousness, he smoked a new "resin," which he believed contained cannabis. He required two doses of 400 µg IV naloxone before regaining consciousness. Two hours after admission in the ED, he required an additional 800 µg of IV naloxone due to respiratory depression. He required 12-h naloxone infusions before discharge [33]	Peripheral blood	Isotonitazene (0.81 ng/mL)	Cocaine Buprenorphine metabolites	N/A

Table 2 continued

Case	Pertinent history	Blood source	Synthetic opioid found	Additional findings	Cause of death
11. Shanks et al., 2017	28 y/o M with a history of heroin use was found decease in his jail bed. History suggested heroin use the previous night. Autopsy revealed pulmonary edema [33]	Iliac blood	Carfentanil (23.3 ng/L)	11-nor-9-carboxy-delta-9-tetrahydrocannabinol (9.6 µg/L)	Acute carfentanil intoxication
Additional Case Studies					
12. Shanks et al., 2017	26 y/o F with a history of drug use was found deceased following heroin use the night prior [33]	Iliac blood	Carfentanil (234 ng/L)	11-nor-9-carboxy-delta-9-tetrahydrocannabinol (10.1 µg/L) Topiramate (7.5 mg/L)	Carfentanil intoxication
13. Shanks et al., 2017	36 y/o F with a history of drug use was found unresponsive in her bedroom surrounded by drug paraphernalia. Autopsy showed frothy pulmonary edema [33]	Femoral blood	Carfentanil (107 ng/L)	THC (4.9 µg/L) 11-nor-9-carboxy-delat-9-tetrahydrocannabinol (67.5 µg/L)	Carfentanil toxicity
14. Shanks et al., 2017	25 y/o M with a history of drug use was in full rigor mortis with a white frothy foam and purge fluids around his mouth and ears. There was vomit and other bodily fluids on the floor surrounding the bed. He had a capped syringe in his pants pocket. Autopsy revealed pulmonary edema and track marks on the body [33]	Heart blood	Carfentanil (24 ng/L)	Carfentanil (24 ng/L) Benzoylecgonine (54.3 µg/L) Naloxone Caffeine	Cocaine and carfentanil intoxication
15. Shanks et al., 2017	44 y/o F with a history of alprazolam and heroin use was found deceased. No autopsy was performed [33]	Femoral blood	Carfentanil (105 ng/L)	Cotinine	Carfentanil intoxication

Table 2 continued

Case	Pertinent history	Blood source	Synthetic opioid found	Additional findings	Cause of death
16. Shanks, et al., 2017	44 y/o M with a history of heroin and ethanol use was found unresponsive. He was previously prescribed numerous prescription medications including alprazolam, atorvastatin, ondansetron, phenytoin, quetiapine, and ibuprofen. Attempts at resuscitation including naloxone were unsuccessful. Significant autopsy findings included needle puncture sites on the bilateral arms and lung findings suggestive of asthmatic type of bronchitis [33]	Femoral blood	Carfentanil (114 ng/L) Furanyl fentanyl (0.61 µg/L)	Alprazolam (3.4 µg/L) Codeine (40.0 µg/L) Buprenorphine (0.6 µg/L) Phenytoin (4.0 mg/L) Quetiapine (370 µg/L) Naloxone Nicotine Cotinine	Multiple drug intoxication
17. Shanks, et al., 2017	50 y/o M was found unresponsive in his parked truck and pronounced dead at a local hospital. Autopsy showed severe pulmonary congestion and edema, asymmetric cardiac hypertrophy, congestive splenomegaly, steatosis of the liver, and left adrenal adenoma [33]	Subclavian blood	Carfentanil (617 ng/L) Fentanyl (2.9 µg/L)	Ethanol (0.2 g/L) (urine) Fentanyl (urine), norfentanyl (urine)	Fentanyl and carfentanil toxicity
18. Shanks et al., 2017	27 y/o M who had been living in his car was brought into the hospital by a friend where he was ultimately pronounced dead. Autopsy was not performed [33]	Femoral blood	Carfentanil (529 ng/L)	11-nor-9-carboxy-delta-9-tetrahydrocannabinol (10.1 µg/L) 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (urine) Fentanyl (urine) Norfentanyl (urine) Morphine (urine)	Carfentanil toxicity

Table 2 continued

Case	Pertinent history	Blood source	Synthetic opioid found	Additional findings	Cause of death
19. Shanks, et al., 2017	62 y/o F with history of illicit and prescription drug use including heroin and fentanyl was found deceased in her home. Her prescribed medications include sertraline, clonidine, tramadol, gabapentin, and lisinopril. No autopsy was performed [33]	Femoral blood	Carfentanil (45.7 ng/L) Fentanyl (1.1 µg/L)		Carfentanil and fentanyl toxicity
20. Shanks, et al., 2017	39 y/o M with a history of heroin use was found unresponsive outside his vehicle and subsequent attempts at resuscitation were unsuccessful. Autopsy showed include track marks on the hands and arms, congested edematous lungs, evidence of hypertensive heart disease with enlarged heart and thickened left ventricles, and hepatic steatosis [33]	Femoral blood	Carfentanil (10.4 ng/L)	Ethanol (1.54 g/L) Amitriptyline (29.9 µg/L) Nicotine Cotinine	Mixed drug intoxication
21. Papsu et al., 2022	27 y/o M was found deceased surrounded by drug paraphernalia, vials filled with unknown powders, orange pills, and marijuana [34]	Femoral blood	Isotonitazene (1.5 ng/mL)	Delta-9 THC (7.6 ng/mL) THCC (81 ng/mL) 11-hydroxy 11 hydroxy THC (3.0 ng/mL) Venlafaxine (92 ng/mL) O-desmethylvenlafaxine (580 ng/mL)	Acute venlafaxine and isotonitazene intoxication
22. Papsun et al., 2022	83 y/o M with a history of exchanging sexual favor for drugs was found unresponsive in a hotel room. Another woman was also found unresponsive in the bathroom. Heroin and fentanyl were found in her purse [34]	Iliac blood	Isotonitazene (1.6 ng/mL)	Donepezil (7.8 ng/mL)	Unavailable

Table 2 continued

Case	Pertinent history	Blood source	Synthetic opioid found	Additional findings	Cause of death
23. Papsun et al., 2022	59 y/o M with a history of drug use and recent cocaine overdose was found unresponsive. Autopsy showed cerebral edema, pulmonary congestion, and edema in addition to cardiac pathology [34]	Peripheral blood	Isotonitazene (0.68 ng/mL)		Isotonitazene intoxication complicated by coronary atherosclerosis and dilated cardiomyopathy
24. Papsun et al., 2022	33 y/o F with a history of heroin and methamphetamine use was discovered face down on the floor. She was unresponsive with partially digested food in her mouth and on her lips [34]	Iliac blood	Brorphine (1.1 ng/mL)	Ethanol (83 mg/dL)	Combined brorphine and ethanol toxicity
25. Papsun et al., 2022	26 y/o M male was found unresponsive by emergency medical services (EMS) and transported to the ED where he was pronounced dead despite attempted resuscitation. He appeared to have excess mucus production from the nose and mouth with evidence of white powder. Autopsy showed cerebral and pulmonary edema [34]	Peripheral blood	Brorphine (0.56 ng/mL)	Benzoylecgonine (120 ng/mL)	Combination brorphine and cocaine toxicity
26. Papsun et al., 2022	59 y/o F was found deceased outside an abandoned building. Autopsy revealed mild pulmonary edema and atherosclerotic/hypertensive cardiovascular disease [34]	Peripheral blood	Brorphine (12 ng/mL)	Ethanol (144 mg/dL)	Brorphine and ethanol toxicity

Table 2 continued

Case	Pertinent history	Blood source	Synthetic opioid found	Additional findings	Cause of death
27. Papsun et al., 2022	28 y/o M with known history of substance use was found deceased in bed with pink foam surrounding his mouth. He was surrounded by drug paraphernalia including a spoon, metal plate, pipe, grinder, and white powder subsequently determined to be AP-238. His prescription medications included fluoxetine, alprazolam, and pain medication for an upcoming back surgery [34]	Peripheral blood	AP-238 (270 ng/mL)	Delta-9 THC (16 ng/mL) THCC (110 ng/mL) 11-hydroxydelta-9 THC (6.8 ng/mL) Acetaminophen (18 µg/mL)	Probably drug toxicity with AP-238 and other novel substances
28. Papsun et al., 2022	41 y/o M male with known history of synthetic heroin use was found supine in a shed without signs of trauma. Marijuana, needles, and empty baggies were found at the scene. Autopsy showed pulmonary congestion and edema, cerebral edema, and aspiration of gastric contents [34]	Iliac blood	AP-238 (87 ng/mL)	Methadone (680 ng/mL) EDDP (62 ng/mL) Delta-9 THC (0.87 ng/mL) THCC (18 ng/mL) 11-hydroxy delta-9 THC (1.0 ng/mL) Memantine (590 ng/mL)	Combined methadone and AP-238 toxicity
29. Papsun et al., 2022	49 y/o with known history of substance use was found unresponsive and resuscitation attempts were unsuccessful. Autopsy revealed pulmonary edema and hypertensive cardiovascular changes [34]	Femoral blood	Metonitazene (0.96 ng/mL)	Ethanol (302 mg/mL)	Metonitazene and ethanol toxicity

Table 2 continued

Case	Pertinent history	Blood source	Synthetic opioid found	Additional findings	Cause of death
30. Papsun et al., 2022	20 y/o M male with known history of "molly" and alprazolam use was found deceased. Drug paraphernalia at the scene tested positive for 2-methyl AP-237, clonazolam, and fluoromethylphenidate, and psilocin/psilocybin mushrooms. Autopsy showed biventricular hypertrophy and dilatation, hepatosplenomegaly, and pulmonary congestion and edema [34]	Iliac blood	2-methyl AP-237 (320 ng/mL)	8-aminoclonazole (22 ng/mL) 7-aminoclonazepam (7.6 ng/mL)	2-methyl AP-237 and 8-aminoclonazole toxicity
31. Papsun et al., 2022	F with a known history of drug use was found unresponsive after IV "gray heroin" injection. Autopsy revealed pulmonary edema [34]	Peripheral blood	Metonitazene (7.1 ng/mL)	Delta-9 THC (2.1 ng/mL)	Metonitazene toxicity
32. Papsun et al., 2022	53 y/o M found unresponsive surrounded by needles and baggies with an unknown white powder. Autopsy showed mild pulmonary congestion and edema, as well as hypertensive and atherosclerotic cardiovascular disease [34]	IVC blood	Metonitazene (1.2 ng/mL)	Diphenhydramine (150 ng/mL) gabapentin (17 µg/mL)	Metonitazene toxicity with contributing hypertensive and atherosclerotic cardiovascular disease
33. Papsun et al., 2022	32 y/o F with known history of IV opiate, methamphetamine, and prescription drug use was found unresponsive. Heroin was found at the scene. At the hospital she was diagnosed with an anoxic brain injury with lactic acidosis and status epilepticus. She never regained consciousness and was pronounced dead 5 days later [34]	Peripheral blood	Metonitazene (7.0 ng/mL)		Metonitazene intoxication

Table 2 continued

Case	Pertinent history	Blood source	Synthetic opioid found	Additional findings	Cause of death
34. Papsun et al., 2022	22 y/o M was found deceased in his dorm room with drug paraphernalia including scales with brown and white residues, baggies, liquid syringes, and vape. Testing of the various substances was positive for modafinil, melatonin, valerian root, and propylene glycol [34]	Femoral blood	Etodesnitazene (30 ng/mL)	3-fluorophenmetrazine mitragynine (310 mg/mL) Etizolam (12 ng/mL) Alpha-hydroxyetizolam (14 ng/mL) Amphetamine (370 ng/mL) Gabapentin (6.7 µg/mL) Sertraline (1000 ng/mL) Desmethylsertraline (1200 ng/mL) Olanzapine 38 (ng/mL) Benzoylecgonine (140 ng/mL) Ethanol (12 mg/dL	Mixed drug intoxication
35. Papsun et al., 2022	35 y/o M with a known history of drug and alcohol use and cardiovascular disease was admitted to the hospital in cardiac arrest and subsequently diagnosed with an anoxic brain injury. He never regained consciousness and died 3 days later [34]	Peripheral blood	Metonitazene (1.8 ng/mL)	Ethanol (167 mg/dL)	Hypoxic ischemic encephalopathy from metonitazene and alcohol intoxication with significant contributing factor of ischemic hypertensive cardiovascular disease

Table 2 continued

Case	Pertinent history	Blood source	Synthetic opioid found	Additional findings	Cause of death
36. Papsun et al., 2022	19 y/o M was found unresponsive following known marijuana use. Unmarked tablets found at the scene tested positive for isotonitazene and oxycodone [34]	Femoral blood	Isotonitazene (0.4 ng/mL)	Delta-9 THC (2.1 ng/mL) THC (10 ng/mL)	Isotonitazene toxicity
37. Papsun et al., 2022	61 y/o M was found unresponsive in possession of fentanyl [34]	Peripheral blood	Metonitazene (1.1 ng/mL)	Ethanol (228 mg/dL)	Unavailable
38. Mueller, et al., 2021	An individual with known history of depression, fentanyl use, and previous cardiac arrest was found deceased. White powder found at scene tested positive for isotonitazene. Autopsy showed blood congestion of the organ with gastric material in the upper and lower respiratory tract [35]	Femoral blood	Isotonitazene (2.28 ng/mL)	Diazepam (29 ng/mL) Nordiazepam (71 ng/mL) Oxazepam (4.8 ng/mL) Mefenamic acid Domperidone (6.0 ng/mL) Acetaminophen (4.8 µg/mL)	Acute intoxication with isotonitazene
39. Mueller, et al., 2021	M with a history of reactive depressive syndrome following the death of his brother was found deceased. Autopsy revealed congested organs, alveolar edema, and gastric material in the upper and lower respiratory tract [35]	Femoral blood	Isotonitazene (0.74 ng/mL)	Ethanol (0.57 g/kg)	Acute isotonitazene intoxication

IVC Inferior vena cava

From education of OUD treatment and appropriate guidelines to pharmaceutical advancements, various entities, agencies, and measures can all be simultaneously implemented to effectively treat OUD, reduce addiction, and prevent further substance use. Moreover, raising awareness of the dangers of the new synthetic opioids to those at risk and providing support may reduce the number of fatal overdoses.

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REFERENCES

1. Florence C, Luo F, Rice K. The economic burden of opioid use disorder and fatal opioid overdose in the United States, 2017. Drug Alcohol Depend. 2021;1(218): 108350.

2. Manchikanti L, Singh VM, Staats PS, Trescot AM, Prunskis J, Knezevic NN, et al. Fourth wave of opioid (Illicit Drug) overdose deaths and diminishing access to prescription opioids and interventional techniques: cause and effect. Pain Physician. 2022;25(2):97–124.

3. Volkow ND, Blanco C. The changing opioid crisis: development, challenges and opportunities. Mol Psychiatry. 2021;26(1):218–33.

4. Armenian P, Vo KT, Barr-Walker J, Lynch KL. Fentanyl, fentanyl analogs and novel synthetic opioids: a comprehensive review. Neuropharmacology. 2018;134(Pt A):121–32.

5. Strang J, Volkow ND, Degenhardt L, Hickman M, Johnson K, Koob GF, et al. Opioid use disorder. Nat Rev Dis Primer. 2020;6(1):3.

6. Abuse NI on D. Overdose Death Rates [Internet]. National Institute on Drug Abuse. 2022. https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates. Accessed 28 Oct 2022.

7. Manchikanti L, Vanaparthy R, Atluri S, Sachdeva H, Kaye AD, Hirsch JA. COVID-19 and the opioid epidemic: two public health emergencies that intersect with chronic pain. Pain Ther. 2021;10(1):269–86.

8. Ciccarone D. The rise of illicit fentanyls, stimulants and the fourth wave of the opioid overdose crisis. Curr Opin Psychiatry. 2021;34(4):344–50.

9. Kline A, Mattern D, Cooperman N, Williams JM, Dooley-Budsock P, Foglia R, et al. Opioid overdose in the age of fentanyl: Risk factor differences among subpopulations of overdose survivors. Int J Drug Policy. 2021;90: 103051.

10. National Drug Threat Assessment [Internet]. Report No.: DEA-DCT-DIR-008–21. 2021. https://www.dea.gov/sites/default/files/2021-02/DIR-008-21%202020%20National%20Drug%20Threat%20Assessment_WEB.pdf

11. Han Y, Yan W, Zheng Y, Khan MZ, Yuan K, Lu L. The rising crisis of illicit fentanyl use, overdose, and potential therapeutic strategies. Transl Psychiatry. 2019;9(1):282.

12. Skolnick P. Treatment of overdose in the synthetic opioid era. Pharmacol Ther. 2022;233: 108019.

13. HAN Archive - 00438 | Health Alert Network (HAN) [Internet]. 2021. https://emergency.cdc.gov/han/2020/han00438.asp. Accessed 28 Oct 2022.

14. Blecha JE, Henderson BD, Hockley BG, VanBrocklin HF, Zubieta JK, DaSilva AF, et al. An updated synthesis of [11C]carfentanil for positron emission tomography (PET) imaging of the μ-opioid receptor. J Label Compd Radiopharm. 2017;60(8):375–80.

15. Zawilska JB, Kuczyńska K, Kosmal W, Markiewicz K, Adamowicz P. Carfentanil: from an animal anesthetic to a deadly illicit drug. Forensic Sci Int. 2021;320: 110715.

16. Jalal H, Burke DS. Carfentanil and the rise and fall of overdose deaths in the United States. Addiction. 2021;116(6):1593–9.

17. Flynn SM, France CP. Discriminative stimulus effects of carfentanil in rats discriminating fentanyl: Differential antagonism by naltrexone. Drug Alcohol Depend. 2021;221: 108599.

18. Bardsley R. Higher naloxone dosing may be required for opioid overdose. Am J Health Syst Pharm. 2019;76(22):1835–7.

19. Critical Review Report: Protonitazene [Internet]. Geneva: World Health Organization (Expert Committee on Drug Dependence); 2022; pp. 1–16. https://cdn.who.int/media/docs/default-source/controlled-substances/45th-ecdd/protonitazene_draft.pdf?sfvrsn=dfb007b3_1

20. Schumann JL, Syrjanen R, Alford K, Mashetty S, Castle JW, Rotella J, et al. Intoxications in an Australian Emergency Department Involving "Nitazene" benzylbenzimidazole synthetic opioids (etodesnitazene, butonitazene and protonitazene). J Anal Toxicol. 2022. https://doi.org/10.1093/jat/bkac062.

21. Protonitazene [Internet]. Overdose Prevention Strategies. https://www.overdosepreventionstrategies.org/glossary/protonitazene/. Accessed 22 Oct 2022.

22. Protonitazene: Stronger than Fentanyl | Healthy Life Recovery [Internet]. 2022 https://healthyliferecovery.com/protonitazene-new-synthetic-opioid/. Accessed 22 Oct 2022.

23. De Luca MA, Tocco G, Mostallino R, Laus A, Caria F, Musa A, et al. Pharmacological characterization of novel synthetic opioids: Isotonitazene, metonitazene, and piperidylthiambutene as potent μ-opioid receptor agonists. Neuropharmacology. 2022;221: 109263.

24. New, Dangerous Synthetic Opioid in D.C., Emerging in Tri-State Area [Internet]. https://www.dea.gov/stories/2022/2022-06/2022-06-01/new-dangerous-synthetic-opioid-dc-emerging-tri-state-area. Accessec 23 Oct 2022.

25. Shover CL, Falasinnu TO, Freedman RB, Humphreys K. Emerging characteristics of isotonitazene-involved overdose deaths: a case-control study. J Addict Med. 2021;15(5):429–31.

26. Morris NP. Opioid use disorder treatment in the age of fentanyl. JAMA Intern Med. 2022;182(3):249–50.

27. Buprenorphine Treatment of Fentanyl-Related Opioid Use Disorder | Psychiatrist.com [Internet]. 2022. https://www.psychiatrist.com/pcc/addiction/substance-use-disorders/buprenorphine-treatment-fentanyl-related-opioid-use-disorder/. Accessed 0 Oct 2022.

28. Comer SD, Cahill CM. Fentanyl: Receptor pharmacology, abuse potential, and implications for treatment. Neurosci Biobehav Rev. 2019;106:49–57.

29. Buresh M, Nahvi S, Steiger S, Weinstein ZM. Adapting methadone inductions to the fentanyl era. J Subst Abuse Treat. 2022;141: 108832.

30. Varshneya NB, Thakrar AP, Lambert E, Huhn AS. Opioid use disorder treatment in the fentanyl era. J Addict Med. 2022. https://doi.org/10.1097/ADM.0000000000001013.

31. Manchikanti L, Hirsch JA. Comment on "trends in and characteristics of buprenorphine misuse among adults in the U.S." Pain Physician. 2022;25(4):E697.

32. Dayer LE, Painter JT, McCain K, King J, Cullen J, Foster HR. A recent history of opioid use in the US:

three decades of change. Subst Use Misuse. 2019;54(2):331–9.

33. Shanks KG, Behonick GS. Detection of Carfentanil by LC–MS-MS and Reports of Associated Fatalities in the USA. J Anal Toxicol. 2017;41(6):466–72.

34. Papsun DM, Krotulski AJ, Logan BK. Proliferation of novel synthetic opioids in postmortem investigations after core-structure scheduling for fentanyl-related substances. Am J Forensic Med Pathol. 2022. https://doi.org/10.1097/PAF.0000000000000787.

35. Mueller F, Bogdal C, Pfeiffer B, Andrello L, Ceschi A, Thomas A, et al. Isotonitazene: fatal intoxication in three cases involving this unreported novel psychoactive substance in Switzerland. Elsevier enhanced reader. Forensic Sci Int. 2021. https://doi.org/10.1016/j.forsciint.2021.110686.

36. Swanson DM, Hair LS, Strauch Rivers SR, Smyth BC, Brogan SC, Ventoso AD, et al. Fatalities involving carfentanil and furanyl fentanyl: two case reports. J Anal Toxicol. 2017;41(6):498–502.

37. De Baerdemaeker KSC, Dines AM, Hudson S, Sund LJ, Waters ML, Hunter LJ, et al. Isotonitazene, a novel psychoactive substance opioid, detected in two cases following a local surge in opioid overdoses. QJM Int J Med. 2022. https://doi.org/10.1093/qjmed/hcac039.

38. Mueller F, Bogdal C, Pfeiffer B, Andrello L, Ceschi A, Thomas A, et al. Isotonitazene: Fatal intoxication in three cases involving this unreported novel psychoactive substance in Switzerland. Forensic Sci Int. 2021;1(320): 110686.

39. Zilg B, Thelander G, Giebe B, Druid H. Postmortem blood sampling—comparison of drug concentrations at different sample sites. Forensic Sci Int. 2017;1(278):296–303.

40. King AMD, Foley D, Arfken C, Aaron CMD, Sung LMD, Hlavaty LMD. Carfentanil-Associated Mortality in Wayne County, Michigan, 2015–2017. Am J Public Health. 2019;109(2):300–2.

41. McCranor BJ, Jennings L, Tressler J, Tuet WY, DeLey Cox VE, Racine M, et al. Assessment of naloxone as a therapeutic for inhaled carfentanil in the ferret. Toxicol Rep. 2020;22(7):1112–20.

42. DEA Issues Carfentanil Warning To Police And Public [Internet]. 2022. https://www.dea.gov/press-releases/2016/09/22/dea-issues-carfentanil-warning-police-and-public. Accessed 04 Nov 2022.

43. Lust EB, Barthold C, Malesker MA, Wichman TO. Human health hazards of veterinary medications: information for emergency departments. J Emerg Med. 2011;40(2):198–207.

44. Urits I, Li N, Berardino K, Artounian KA, Bandi P, Jung JW, et al. The use of antineuropathic medications for the treatment of chronic pain. Best Pract Res Clin Anaesthesiol. 2020;34(3):493–506.

45. Nagireddi JN, Vyas AK, Sanapati MR, Soin A, Manchikanti L. The analysis of pain research through the lens of artificial intelligence and machine learning. Pain Physician. 2022;25(2):E211–43.

46. Soin A, Hirschbeck M, Verdon M, Manchikanti L. A pilot study implementing a machine learning algorithm to use artificial intelligence to diagnose spinal conditions. Pain Physician. 2022;25(2):171–8.