

Causes, Nature and Toxicology of Fentanyl-Analogues Associated Fatalities: A Systematic Review of Case Reports and Case Series

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Objective: Mortalities due to fentanyl derivatives are on the rise with novel fentanyl analogues and still emerging on the global illicit drug market. They are highly potent and very fatal in low doses, yet there has been a lack of systematic research surrounding this subject. This review aims to assess the causes, nature, and toxicology of fatalities associated with fentanyl analogues.

Methods: Five databases: Scopus, Embase, Medline, PubMed and Google Scholar were searched from inception to October 2020 to identify case studies and case series reporting fentanyl analogue-related fatalities. Two independent reviewers screened and selected the articles followed by the data extraction from each article, which included demography, route of administration, causes and nature of death, and the fentanyl analogue implicated. All articles were then subject to quality assessment tools developed by the Joanna Briggs Institute (JBI). A narrative synthesis was undertaken.

Results: The initial data search yielded 834 articles, only 14 of which met the inclusion criteria – this included nine case reports and five case series. Of the 1079 fentanyl-analogue related deaths reported, the majority of them occurred in the US (n=1044, 96.8%). The majority of fatalities were male (n=766, 71%), white (n=884, 87%) and in the age ranges 25–34 and 35–44 years (30.5% and 29.6%, respectively). The most common route of administration was intravenous (n=319, 66%) and the manner of death was almost exclusively accidental (99.7%). The predominant cause of death was fentanyl-analogue toxicity (n=292, 85.4%) and involved mixed drug toxicity (n=47, 13.7%). The mean post-mortem fentanyl analogue concentration was 31.6 ng/mL.

Conclusion: Most fatalities were reported in the US involving young white males. Overdose through intravenous administration and by mixed drug toxicities with other opioids were the major causes of death. Deaths reported in peer-reviewed literature were relatively less than those reported by real-world data.

Keywords: fentanyl-analogues, fatalities, systematic review, case series, case reports

Introduction

Fentanyl and its analogues are synthetic opioid analgesics which act as full agonists for the μ -opioid receptor.¹ Fentanyl itself is 50–100 times more potent than morphine and one of its analogues, carfentanyl, is estimated to be 10,000 times more potent.¹ They are of the phenylpiperidine family and were synthesized through modifications of the pethidine (meperidine) structure.² Pharmacokinetic properties of fentanyl and its analogues include a highly lipid-soluble structure,

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that allows for effective and rapid diffusion across the blood–brain barrier, contributing to a rapid onset of effects in the central nervous system.¹ This makes them effective in the management of moderate to severe pain in human and veterinary medicine. However, as with other opioids, possible adverse effects include: respiratory depression, bradycardia, nausea and vomiting, and muscle rigidity of the chest wall or jaw.^{3–6} Timely administration of the antidote naloxone can reverse the effects of respiratory depression after the overdose, however, larger and more frequent administrations may be required due to the increased potency of fentanyl analogues compared to other opioids such as heroin.

As with opioids such as morphine, codeine and oxycodone, fentanyl and its analogues have the potential for misuse. This could either be in the form of abusing licensed and prescribed fentanyls (such as alfentanil, remifentanil and sufentanil) or the use of illicitly manufactured fentanyls (IMF). Both have been implicated in a large number of fatal overdoses worldwide, but particularly concentrated in the United States (US) where the opioid crisis was declared a nationwide public health emergency in 2017.⁷ While the use of the above prescribed fentanyls are restricted to use within hospital and restricted settings, illegal import, manufacturing and distribution remains a key concern.⁸

The US is visibly at the center of the world's opioid crisis with drug overdose deaths exceeding those attributable to firearms, car accidents, homicides, or HIV/AIDS.⁹ This epidemic may be traced back to the mid-1990s when drug companies, such as Purdue Pharma, began promoting their opioid products, prompted by the newly manufactured OxyContin.¹⁰ OxyContin was widely marketed to effectively alleviate chronic pain with minimal side effects and a low potential for addiction which was later contested, resulting in a US\$ 635 million fine for Purdue Pharma in 2007.¹¹ Nonetheless, this led to a decades-long culture of large-scale commercial advertising of the opioids to the general public and physicians, even lobbying lawmakers and sending representatives to individual doctors to promote their benefits.¹² However, concerns were raised by some experts about the expertise of primary care prescribers in pain management or addiction issues.¹³ Additionally, in the US there is direct advertising of pharmaceuticals to consumers, encouraging them to ask doctors for specific drugs.¹⁴ Furthermore, a significant proportion of these doctors are in private practice where

patient satisfaction is paramount because there is a great financial benefit in the number of returning patients.

Time trend analysis further confirms deepening opioid crisis in the US.⁸ Opioid-involved overdose deaths in the US have shown steady rise from 18, 515 deaths in 2007 to 47,600 in 2017, an increase of 157%.¹⁵ Rates of overdose deaths involving synthetic opioids other than methadone, which includes fentanyl, increased 10% from 2017 to 2018 with over 31, 000 people dying in 2018.¹⁶ The Centre for Disease Control and Prevention (CDC) suggests that much of this increase may be due to illegally or illicitly made fentanyls.¹⁷ Nonetheless, more recently the US has introduced prescription drug monitoring programs for strict monitoring of the prescribing trends.¹⁸ Prescription drug monitoring programs (PDMPs) are statewide databases in the US that track the controlled drugs dispensing and are accessible to those prescribing and dispensing the drugs as well as to the law enforcement organizations and regulatory bodies.¹⁹

Many of these opioid overdoses are thought to be unintentional and as a result of contamination of the illicit drug supply on the streets. Illicit contamination with fentanyls is not limited to heroin or counterfeit prescription-strength opioid pills - in 2016, three patients died and nine were admitted to hospital after unknowingly taking cocaine that had been laced with fentanyl.²⁰ This is particularly concerning because a proportion of cocaine users are opioid-naïve which would likely result in accidental overdose. Furthermore, fentanyl analogues only require marginal doses before resulting in overdose, accentuating their risk.

Outside the US, there is also an increasing trend in the prevalence of opioid including fentanyl use and associated harm in Europe.^{21,22} In 2017, 1300 new synthetic opioids (NSOs) were seized by law enforcement, 72% of which were fentanyl derivatives.²³ In 2018, fake Xanax and OxyContin tablets were found to contain fentanyls in Denmark and Sweden,²³ similar to the previously mentioned incidents that occurred in the US.²⁰ The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) also reported more than 250 deaths linked to fentanyls in Europe in 2016–17.²³ Lamentably, many fentanyl analogue deaths are also believed to be unreported because, although fentanyl analogues are similar in structure to fentanyl, they are not routinely detected as specialized toxicology testing is required for their precise detection.²⁴

Novel fentanyl analogues have been steadily emerging on the illicit drug market, posing a migrating global public health risk. The highly potent and lethal nature of fentanyl analogues has implicated them in countless deaths worldwide, taking into account the many that are undetected and unreported. A systematic review highlighting the mortality associated with fentanyl has been published,²⁵ however, no review has been conducted regarding fentanyl analogues. Therefore, this review aimed to assess the causes, nature and toxicology of fentanyl-analogue associated fatalities using case reports and case series.

Methods

Data Search

A systematic search strategy was employed in this review. Five databases (comprised of Scopus, Embase, Medline, PubMed and Google Scholar) were used to conduct an initial broad search of entries from inception to October 2020 related to deaths associated with fentanyl analogues. The search terms used were “fentanyl-analogue”, “deaths”, “mortality”, “fatality”, “case report”, “case series” and other relevant synonyms.

Study Selection

Studies were eligible for inclusion if they were case reports or case series that examined fentanyl-analogue related deaths of adults (aged 15 years or above) and were reported in the English Language. Articles focusing solely on fentanyl itself and novel synthetic opioids (NSOs) were excluded from the review.

Data Extraction and Quality Assessment

A data extraction table was developed which summarized the key information from each article, including demography, route of administration, cause and nature of death, and the fentanyl analogue implicated (Table 1).

Quality Assessment

All articles were subject to one of the two quality assessment tools developed by the Joanna Briggs Institute (JBI). These tools correlated to either case studies or case series but both were used to critically appraise the results and methodology used within the studies.²⁶

Data Synthesis and Analysis

The independent extraction of data was undertaken by two reviewers (UR, EC). A narrative synthesis was conducted

due to the differences and variability within the objectives and results of each study.

Ethics Statement

This review did not require ethical approval.

Results

The data search yielded 834 results which were subsequently narrowed down after removing duplications and irrelevant articles. Twenty-nine articles were screened at the full text (including articles found using their bibliographies), resulting in 14 articles – nine case reports and five case series.^{24,27–39} (see Figure 1).

Generally, the case reports were of very good quality clearly describing the demographical information and demonstrating a clear timeline of events. Diagnostic tests for the fentanyl analogues were clearly described by eight out of nine case reports and the majority concluded a clear takeaway message (Table 2).

The quality of the case series was varied with only one out of five articles reporting clinical information of participants and three having a robust consecutive inclusion criterion for their case series. Demographical information for the relevant geographical area could also have been improved in some cases. However, the demographics of participants themselves were well reported, and most statistical analyses were appropriate (Table 3).

Demography

A total of 1079 fentanyl-analogue related deaths were reported in the included studies. The vast majority of these deaths occurred in the USA (n=1044, 96.8%). This was followed by UK (n=32, 3%), France (n=1, <0.1%), Switzerland (n=1, <0.1%) and Western Australia (n=1, <0.1%). The majority (71%) of the total number of deaths were male (n=766). The highest number of deaths were in the age ranges 25–34 and 35–44 years (30.5% and 29.6%, respectively). Of the ethnicities that were reported, 87% of deaths were among white (n=884), 10% black (n=101), 2% Hispanic (n=20) and 1% “other” (n=9) individuals.

Routes of Administration

Approximately half of the incidents (n=483) clearly reported route of administration or could be inferred from the data provided. The most common route of administration was intravenous (n=319, 66%), followed by inhalation/snorting (n=97, 20%), ingestion (n=41, 8.5%), smoking (n=25, 5.2%) and intralingual (n=1, 0.2%).

Table 1 Characteristics of Included Case Reports and Case Series

Study ID	Country	No. of Fentanyl-Analogue Death Cases Reported	Study Design	Source of Death	Inferred Route of Administration	Cause of Death	Nature of Death
Brockbals et al 2019 ²⁷	Switzerland	n=1 • Male • Age: 39	Case report	Cyclopropylfentanyl	Inhalation	Combined intoxication with ethanol and cyclopropylfentanyl	Unspecified
Butler et al 2017 ²⁸	USA	n=3 • Male: 3 • Age range: 23–43	Case report	Acrylfentanyl Furanylfentanyl	Intravenous (n=3)	Acrylfentanyl toxicity (n=1) Toxic effects of acrylfentanyl and hydrocodone (n=1) Acrylfentanyl and furanylfentanyl toxicity (n=1)	Accidental (n=3)
Castellino et al 2020 ²⁹	USA	n=2 • Male: 2 • Age range: 24–25 • Caucasian	Case report	Cyclopropylfentanyl	Not specified	Cyclopropylfentanyl overdose (n=1) Mixed drug toxicity (n=1)	Accidental (n=2)
Corsi et al 2019 ³⁰	USA	n=17 • Male: 15 Female: 2 • Age range: 21–51 • Caucasian: 15 • African-American: 2	Case series	Carfentanil	Intravenous (n=5) Undetermined (n=12)	Drug abuse (n=10) Drug intoxication (n=6) Drug overdose (n=1)	Suicide by overdose (n=1) Undetermined (n=17)
Daniulaityte et al 2017 ³¹	USA	n=281 • Male: 181 Female: 100 • Age range: • White, non-Hispanic: 257 • Black or other: 24	Case series	Fentanyl Norfentanyl Acrylfentanyl Furanylfentanyl Carfentanil	Unspecified	Drug overdose (n=281)	Accidental (n=281)
Elliott et al 2018 ³²	UK	n=7 • Male: 5 Female: 2 • Age range: 29–44	Case series	Carfentanil	Intravenous (n=1) Not specified (n=6)	Mixed drug toxicity (n=7).	Undetermined but hinted to be accidental
Fagiola et al 2018 ³³	USA	n=5 • Male: 4 Female: 1 • Age ranges: 19–49 • White: 5	Case report	Cyclopropylfentanyl	Intravenous (n=1) Inhalation (n=1) Unspecified (n=3)	Mixed drug toxicity (n=5)	Accidental (n=5)
Gaulier et al 2019 ³⁴	France	n=1 • Male • Age: 41	Case report	Carfentanil	Intralingual	Mixed drug toxicity	Accidental
Hikin et al 2018 ³⁵	UK	n=25 • Male: 22 Female: 3 • Age range: 21–54	Case series	Carfentanil Butyryl fentanyl 4F-butyryl fentanyl Furanyl fentanyl	Unspecified	Mixed drug toxicity (n=25)	Unspecified
Krotulski et al 2017 ³⁶	USA	n=1 • Male • Age: 31 • White	Case report	Tetrahydrofuran- fentanyl	Intravenous	Mixed drug toxicity	Accidental
Moss et al 2019 ³⁷	Western Australia	n=1 • Male • Age: 24	Case report	Acetylfentanyl	Intravenous	Acetylfentanyl toxicity	Accidental

(Continued)

Table 1 (Continued).

Study ID	Country	No. of Fentanyl-Analogue Death Cases Reported	Study Design	Source of Death	Inferred Route of Administration	Cause of Death	Nature of Death
O'Donnell et al 2017 ²⁴	USA	n=720 <ul style="list-style-type: none"> • Male: 520 Female: 200 • Age range: <15 – >65 • White, non-Hispanic: 602 • Black, non-Hispanic: 75 • Other, non-Hispanic: 9 • Hispanic: 20 	Case series	Carfentanil Furanylfentanyl Acetylfentanyl	Intravenous (n=303) Inhalation (n=95) Ingestion (n=41) Smoking (n=25) Unspecified (n=279)	<ul style="list-style-type: none"> • Fentanyl analogue toxicity • Mixed drug/polydrug toxicity • Specific numbers unclear 	Unspecified
Shanks et al 2017 ³⁸	USA	n=13 <ul style="list-style-type: none"> • Male: 8 Female: 5 • Age range: 25–62 	Case report	Carfentanil	Intravenous (n=3) Unspecified (n=10)	Carfentanil drug toxicity (n=7) Mixed carfentanil and fentanyl toxicity (n=2) Mixed drug intoxication (n=4)	Accidental (n=13)
Swanson et al 2017 ³⁹	USA	n=2 <ul style="list-style-type: none"> • Male: 2 • Age range: 25–34 • White: 2 	Case report	Carfentanil Furanylfentanyl	Intravenous (n=1) Unspecified (n=1)	Mixed drug toxicity (n=1) Carfentanil overdose (n=1)	Accidental (n=2)

Nature of Deaths

The nature of death was only reported in 310 deaths out of the included 1079. Of these 310, approximately all were accidental (99.7%) with one classed as suicide by overdose.

Cause of Deaths

The cause of death was only clearly reported in 342 cases. The most predominant cause of death was toxicity due to the fentanyl analogue alone (n=292, 85.4%), followed by mixed drug toxicity (n=47, 13.7%), combined intoxication with a fentanyl analogue and fentanyl (n=2, 0.6%) and combined intoxication with two fentanyl analogues (n=1, 0.3%). Causes of death involving ethanol were classed as mixed drug toxicity. One study reported five decedents having pre-existing medical conditions that may have contributed to their cause of death.³⁰ However, the official causes of death that were reported by this case series were vaguely determined as “drug abuse” (n=10), “drug intoxication” (n=6) and “drug overdose” (n=1). Therefore, these causes were excluded from this analysis.

The most common concomitant drugs used where the deaths were reported due to mixed drug toxicity were opioids, with the most prevalent being heroin, morphine, and oxycodone (Table 4). Other classes of drugs that were used concomitantly included CNS stimulants (such as cocaine and

methamphetamine), benzodiazepines, anti-depressants, and anti-epileptics. Corsi et al examined 17 fatal overdoses involving carfentanil and found that there was not a single case with only carfentanil in the bloodstream.³⁰

Toxicology

Post-mortem fentanyl analogue concentrations were reported in nine out of 14 studies. The range of concentrations was very wide, 0.0104–400 ng/mL (mean 31.6 ng/mL; median 0.340 ng/mL). When excluding two significant outliers this range becomes 0.0104 to 82 ng/mL (mean 6.55 ng/mL; median 0.320 ng/mL). Moss et al acknowledged the relatively high concentration of 400 ng/mL acetylfentanyl in the deceased as being unusual.³⁷

Variation in fentanyl analogue blood toxicology was expected due to the nature and structure of individual fentanyl analogues, the cause of death, the route of administration, the site of blood withdrawal and the degree of opioid tolerance of the deceased.

There were no significant trends in the post-mortem blood toxicology findings when considering the different fentanyl analogues (Table 5), although this could be due to a lack of sufficient data. Although fentanyl analogues share a similar basic chemical structure, subtle differences can impact their chemical and pharmacological properties. For example, higher logP values, which direct the lipophilicity of the drug, will

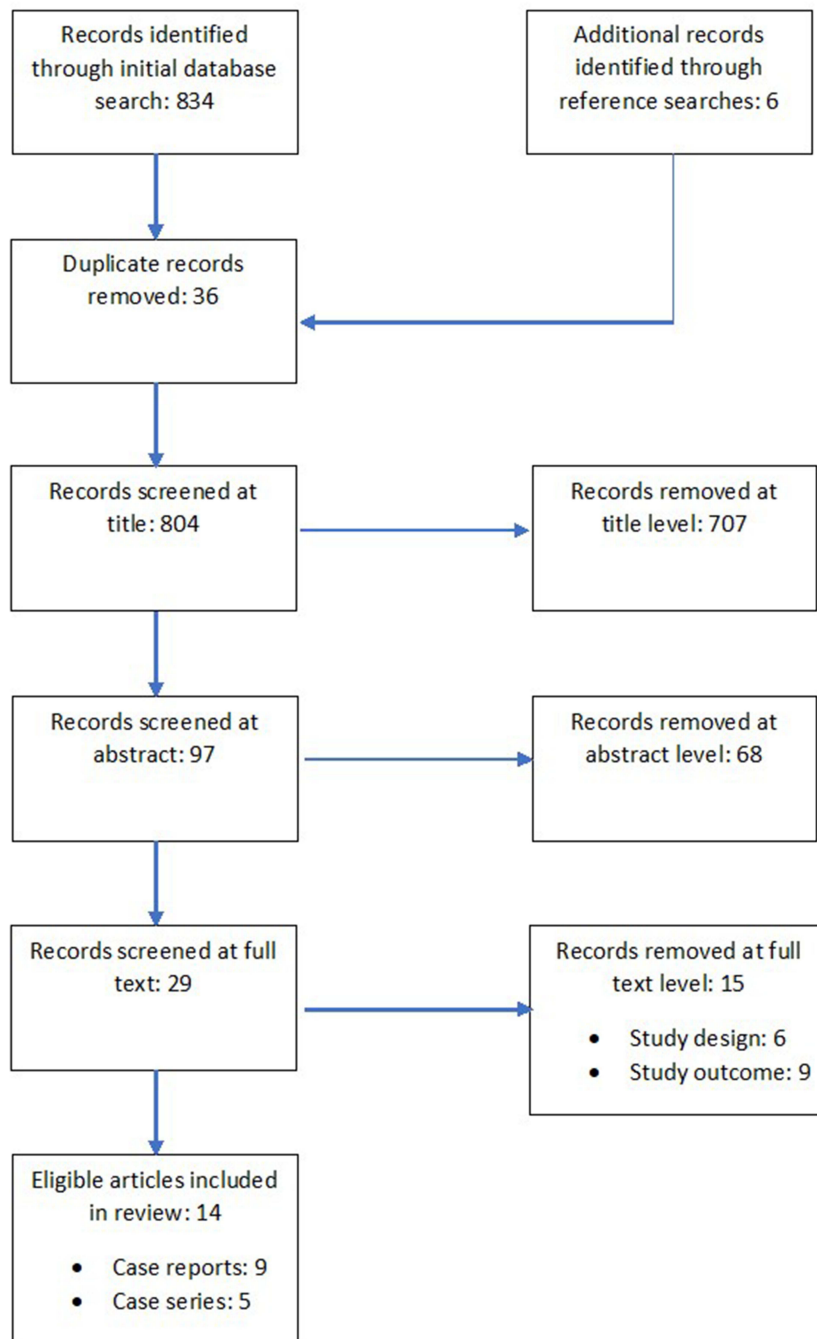


Figure 1 PRISMA flow diagram.

Notes: PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of Clinical Epidemiology*. 2009;62(10):e1-e34. Creative Commons.

allow for rapid diffusion across membranes such as the blood–brain barrier, as previously stated. Drugs with a high logP value, a high volume of distribution ($V_d > 3L/kg$) and that are a base are likely to undergo post-mortem redistribution (PMR).⁴⁰ PMR is the change in drug concentration from a high concentration to a low concentration after death. Fentanyl has been reported to undergo extensive PMR,⁴⁰

however, pharmacological data on fentanyl analogues is lacking and, therefore, such inferences cannot yet be made for them. However, if they do undergo significant PMR, the blood toxicology results retrieved from the included articles should be reviewed because the site and timing of blood withdrawal may have influenced the blood concentrations that were recorded.

Table 2 Quality Assessment of Included Case Reports

	Brockbals et al 2019²⁷	Butler et al 2017²⁸	Castellino et al 2020²⁹	Fagiola et al 2018³³	Gaulier et al 2019³⁴	Krotulski et al 2017³⁶	Moss et al 2019³⁷	Shanks et al 2017³⁷	Swanson et al 2017³⁹
Were patient's demographic characteristics clearly described?	✓	✓	✓	✓	✓	✓	✓	✓	✓
Was the patient's history clearly described and presented as a timeline?	✓	✓	✓	✓	✓	✓	✓	✓	✓
Was the current clinical condition of the patient on presentation clearly described?	✓	✓	✓	✓	✓	✓	✓	✓	✓
Were diagnostic tests or assessment methods and the results clearly described?	✓	✓	✓	✓	✓	✓	✓	✓	✓
Was the intervention(s) or treatment procedure(s) clearly described?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Was the post-intervention clinical condition clearly described?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Were adverse events (harms) or unanticipated events identified and described?	✓	✓	✓	✓	✓	✓	✓	✓	✓
Does the case report provide takeaway lessons?	✓	✓	✓	✓	✓	–	✓	–	✓
Yes	No			Unclear			Not Applicable		
✓	x			–			N/A		

Note: Adapted from Joanna Briggs Institute (JBI).

Discussion

This is the first study of its kind that has reviewed the case reports and case series related to deaths attributed to fentanyl analogues. Nine case reports and five case series involving fatalities associated with various fentanyl analogues were reviewed. The majority of decedents were white males between the ages of 25 and 34 years and living in the United States. The main causes of death were fentanyl analogue overdoses and deaths due to mixed drug toxicity. The most concomitant drugs used in these fatalities were opioids (such as heroin, morphine, and oxycodone) and

a large number also used benzodiazepines and CNS stimulants such as cocaine and methamphetamine. It remains unclear if post-mortem blood fentanyl analogue levels had any correlation with the route of administration or cause of death.

Concurrent drug use by decedents was very common in the included studies. All but two fatalities in the case reports showed evidence of the presence of other drugs in their system at their time of death. Increased tolerance to opioids can and does lead to diversion in the presence of other opioids, seeking out more potent varieties.

Table 3 Quality Assessment of Included Case Series

	Corsi et al 2019 ²³ 30	Daniulaityte et al 2017 ²⁴ 31	Elliott et al 2018 ²⁵ 32	Hikin et al 2018 ²⁸ 35	O'Donnell et al 2017 ¹⁸ 24
Were there clear criteria for inclusion in the case series?	✓	✓	–	✓	✓
Was the condition measured in a standard, reliable way for all participants included in the case series?	✓	✓	✓	✓	✓
Were valid methods used for identification of the condition for all participants included in the case series?	✓	✓	✓	✓	✓
Did the case series have consecutive inclusion of participants?	✓	–	✓	✓	✓
Did the case series have complete inclusion of participants?	✓	✓	–	✓	✓
Was there clear reporting of the demographics of the participants in the study?	✓	✓	✓	–	✓
Was there clear reporting of clinical information of the participants?	✓	✓	✓	✓	✓
Were the outcomes or follow up results of cases clearly reported?	N/A	N/A	N/A	N/A	N/A
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	–	✓	✓	✓	✓
Was statistical analysis appropriate?	–	✓	–	✓	✓
Yes	No		Unclear		Not Applicable
✓	x		-		N/A

Note: Adapted from Joanna Briggs Institute (JBI).

Simultaneous use will produce greater intoxicating effects but will additionally increase the chances of CNS depression and subsequent sedation and possibly even coma or death. These consequences are not only restricted to the concomitant use of opioids with fentanyl analogues but can also be caused by the synergistic effects of benzodiazepines with the use of fentanyls, or antiepileptics with the use of fentanyls by a similar mode of action. The Medicines and Healthcare products Regulatory Agency (MHRA) explicitly states caution in the use of these drugs with opioids due to the potential risk of fatal respiratory depression.^{41,42} Prescribers should always be cautious of signs of drug abuse, dependence, and drug-seeking behavior in their patients before prescribing these drugs. The risk of potentially fatal interactions should be expressly communicated to patients and they should also be aware of signs of dependence. It is important to educate the public on the use of commonly prescribed and readily available drugs because abuse frequently originates with

prescribed opioids before tolerance leads to the seeking out of more potent drugs such as fentanyls.

No firm conclusions can be drawn regarding the influence of the route of administration on post-mortem fentanyl analogue concentrations due to a lack of sufficient data for comparisons. However, it can be safely assumed that fentanyl analogues will follow the same bioavailability principles as other drugs and, therefore, intravenous administration should result in the highest drug concentrations in the blood due to being 100% bioavailable. Drugs administered orally or inhaled will undergo some first-pass metabolism and will demonstrate less than 100% bioavailability, resulting in lower blood concentrations. The extent to which each fentanyl analogue undergoes PMR will also impact on the blood concentrations recorded.

The degree of opioid tolerance at the time of death may be linked to the decedents' blood toxicology recorded. There were only two fentanyl analogue fatalities documented in the included studies which did not

Table 4 Drugs Suspected in Fentanyl Analogues Associated Deaths Classified as a Mixed Drug Toxicity

Drug Class	Drugs Reported in Blood and/or Urine of the Deceased	Total Number Reported in Toxicology	Proportion of Drug Class Which Contributed to Total Fentanyl Analogue Deaths (%)
Anti-depressant /Anti-psychotic	Mirtazapine (n=6) Sertraline (n=6) Amitriptyline (n=2) Olanzapine (n=2) Trazodone (n=2) Aripiprazole (n=1) Clozapine (n=1) Duloxetine (n=1) Nortriptyline (n=1) Paroxetine (n=1) Quetiapine (n=1)	24	2.22
Antiepileptic	Gabapentin (n=15) Pregabalin (n=5) Topiramate (n=2) Phenytoin (n=1)	23	2.13
Antihypertensive	Clonidine (n=1) Lisinopril (n=1) Loperamide (n=1)	3	0.28
Benzodiazepine	Alprazolam Clonazepam Diazepam Nitrazepam Oxazepam Temazepam	107	9.92
	Cannabinoids	113	10.47
CNS stimulants	Cocaine (n=305) Methamphetamine (n=101) Amphetamine (n=4)	410	38.00
Hypnotic/ tranquilizer	Ketamine (n=2) Zolpidem (n=2) Zopiclone (n=2) Zolmitriptan (n=1)	7	0.65
Opioid	Heroin (n=292) Morphine (n=49) Oxycodone (n=32) Methadone (n=21) Codeine (n=18) Hydrocodone (n=17) Tramadol (n=12) Hydromorphone (n=6) Buprenorphine (n=4) Oxymorphone (n=4) Dihydrocodeine (n=2) U-47700 (n=2)	459	42.53
	Phencyclidine	1	0.09

(Continued)

Table 4 (Continued).

Drug Class	Drugs Reported in Blood and/or Urine of the Deceased	Total Number Reported in Toxicology	Proportion of Drug Class Which Contributed to Total Fentanyl Analogue Deaths (%)
Sedating antihistamine	Promethazine (n=2) Chlorpheniramine (n=1) Diphenhydramine (n=1)	4	0.37

Note: Precise Figures For Benzodiazepine Drugs Not Recorded As Some Case Series Recorded Benzodiazepines As Their Own Standalone Category.

have any other concomitant drugs in their blood. Both had died of a carfentanil overdose and their blood toxicology showed their postmortem carfentanil concentrations were lower than the average carfentanil concentration of 0.503 ng/mL (0.221 and 0.105 ng/mL). The lack of concomitant drugs illustrates that carfentanil was solely responsible for their deaths and they may be slightly more opioid naive compared to other decedents whose chronic multidrug use could have increased their levels of opioid tolerance, resulting in the administration of higher fentanyl analogue doses and subsequently higher post-mortem concentrations. It should be emphasized that there is no minimum concentration threshold for a fentanyl analogue to result in death.

In some case reports, the circumstances that the bodies of the decedents were found in suggested that the death was abrupt and unexpected. One such case was reported by Swanson et al where the deceased was found slumped over in the driver's seat of a van that was parked in a car wash, and the car was still running.³⁹ Another instance, described by Fagiola et al, occurred where the decedent was found with a needle still in his arm at a car patrol station³³ and a similar example was reported by Gaulier et al where the individual who was staying at his grandparents' house was found with a 2.5mL syringe still planted under his tongue.³⁴ The reason for such sudden deaths with the intravenous route of administration stems from rapid absorption of the fentanyl analogue across the blood-brain barrier due to its high lipophilicity and 100% bioavailability which exposes the individual to its full effects immediately.

As aforementioned, fentanyl analogues are not routinely screened for in post-mortem toxicology which makes it difficult to notice the trends in drug-related deaths. Even if they are screened for, they are difficult to detect without very sensitive methods of analysis due to their low concentrations in the body resulting from their high potency.

This suggests that there may be many fentanyl analogue associated deaths that are unreported worldwide, leading to many factions underestimating the devastating effects caused by these drugs. Marchei et al reported that liquid chromatography combined with tandem mass spectrometry (LC-MS/MS) and gas chromatography with mass spectrometry (GC-MS) are the most common techniques used to detect fentanyl analogues,⁴³ a detail that is supported by most of the studies included in this review. Both techniques have extremely high specificity and sensitivity. However, they are limited by the continued emergence of new fentanyl analogues of which there are no available reference standards to be used during comparative analyses.⁴⁰ In fact, more than 30 fentanyl analogues have been detected and reported to EMCDDA since 2012,⁴⁴ therefore, experts are unlikely to obtain these reference standards in adequate time before fatalities commence. Alternatively, one potential prospect is the use of liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS) which does not require reference standards when identifying unknown standards and, therefore, this will be beneficial in the fight against new oncoming fentanyl analogues.⁴⁰ However, this technology is limited to few forensic laboratories and is not readily available. Nonetheless, testing for fentanyl analogues should become routine whether using GC/MS, LC-MS/MS or LC-QTOF-MS and the case reports should clearly state if the testing is not employed. This will help account for fentanyl analogue-related deaths that did not involve any testing, as recommended in a report by the ACMD.¹⁴

Strengths and Limitations

This review is the first of its kind in compiling and analyzing peer-reviewed literature on the mortalities associated with fentanyl analogues. The findings related to demography, causes of death, and concurrent drug use are of significant importance. However, this report does have some limitations. Fentanyl analogues are not always

Table 5 Reported Toxicology from Included Case Reports

Fentanyl Analogue	Patient Demographic (Gender, Age)	Route of Administration	Cause of Death	Fentanyl Analogue Concentration (ng/mL) from Specified Blood Source	Evidence of Concomitant Drugs
Acetylfentanyl	Male, 24 [30]	Intravenous	Fentanyl analogue overdose	Source not specified: 400	Yes
Acrylfentanyl	Male, 23 [21]	Intravenous	Fentanyl analogue overdose	Peripheral: 0.3	Yes
	Male, 43 [21]	Intravenous	Mixed drug intoxication	Peripheral: 0.95	Yes
	Male, 26 [21]	Intravenous	Mixed drug intoxication	Peripheral: 0.32	Yes
Carfentanil	Male, 41 [27]	Intralingual	Fentanyl analogue overdose	Source not specified: 4.2	Yes
	Female, 26 [31]	Unspecified	Fentanyl analogue overdose	Iliac: 0.234	Yes
	Male, 38 [31]	Unspecified	Fentanyl analogue overdose	Femoral: 0.221	No
	Female, 36 [31]	Unspecified	Fentanyl analogue overdose	Femoral: 0.107	Yes
	Female, 33 [31]	Unspecified	Mixed drug intoxication	Iliac: 0.145	Yes
	Male, 25 [31]	Intravenous	Mixed drug intoxication	Cardiac: 0.241	Yes
	Female, 44 [31]	Unspecified	Fentanyl analogue overdose	Femoral: 0.105	No
	Male, 28 [31]	Unspecified	Fentanyl analogue overdose	Iliac: 0.0233	Yes
	Male, 38 [31]	Intravenous	Fentanyl analogue overdose	Subclavian: 0.0301	Yes
	Male, 44 [31]	Unspecified	Multiple drug toxicity	Femoral: 0.114	Yes
	Male, 50 [31]	Unspecified	Fentanyl analogue overdose	Subclavian: 0.617	Yes
	Male, 27 [31]	Unspecified	Fentanyl analogue overdose	Femoral: 0.529	Yes
	Female, 62 [31]	Unspecified	Multiple drug toxicity	Femoral: 0.0457	Yes
	Male, 39 [31]	Intravenous	Mixed drug intoxication	Femoral: 0.0104	Yes
	Male, 34 [32]	Intravenous	Mixed drug intoxication	Cardiac: 1.3	Yes
Male, 25 [32]	Unspecified	Fentanyl analogue overdose	Cardiac: 0.12	Yes	

(Continued)

Table 5 (Continued).

Fentanyl Analogue	Patient Demographic (Gender, Age)	Route of Administration	Cause of Death	Fentanyl Analogue Concentration (ng/mL) from Specified Blood Source	Evidence of Concomitant Drugs
Cyclopropylfentanyl	Male, 39 [20]	Inhalation	Mixed drug intoxication	Femoral: 19.8	Yes
	Male, 24 [22]	Unspecified	Fentanyl analogue overdose	Cardiac: present	No
	Male, 25 [22]	Unspecified	Mixed drug intoxication	Cardiac: 14.0	Yes
	Male, 36 [26]	Unspecified	Mixed drug intoxication	Cardiac: 5.6	Yes
	Male, 27 [26]	Inhalation	Mixed drug intoxication	Cardiac: 5.6	Yes
	Male, 32 [26]	Intravenous	Mixed drug intoxication	Cardiac: 29.0	Yes
	Female, 19 [26]	Unspecified	Mixed drug intoxication	Cardiac: 82.0	Yes
	Male, 49 [26]	Unspecified	Mixed drug intoxication	Cardiac: 11.0	Yes
Furanylfentanyl	Male, 34 [32]	Intravenous	Mixed drug intoxication	Cardiac: 0.34	Yes
Tetrahydrofuranlylfentanyl	Male, 31 [29]	Intravenous	Mixed drug intoxication	Source not specified: 339.0	Yes

detected in the routine analysis due to low concentrations in the body because of their high potency and because not all laboratories have the technology to detect them, leading to potentially mass underreporting of fentanyl analogue-related deaths worldwide. This may alter some conclusions drawn by this report. Furthermore, the quality of the included case series was variable. There was a lack of reporting of the clinical conditions of the decedents involved and there were missed opportunities to showcase statistical data to support their findings. Additionally, most studies did not explicitly state the route of administration involved in the fatalities, leading the authors of this review to deduce using their judgement. Therefore, the route of administration must be interpreted cautiously. Finally, unpublished reports have not been included in this review, excluding a valuable source of information.

Implications for Practice and Further Research

Forensic toxicological testing of opioid-involved deaths should be expanded to include fentanyl and fentanyl analogues. Increased efforts to educate the general public and healthcare professionals for the appropriate use of opioids and the recognition of tolerance and dependence should be encouraged and promoted. Where there is evidence of clear chronic drug abuse, all efforts should be used to encourage the

individual to access treatment as these are the persons who are more likely to be adversely affected with fentanyl analogue use. This can be achieved by prescribing medications for opioid use disorders, such as opioid replacement agents (methadone, buprenorphine, levomethadyl) and/or opioid reversal agents (naloxone and naltrexone).⁴⁵ Of the opioid reversal agents, naloxone is FDA approved for acute opioid overdoses whereas naltrexone is used for opioid use disorder with detoxification. Community distribution including take-home naloxone and mail order distribution programs are now in use internationally and such programs have shown to minimize opioid overdose-related deaths.⁴⁶ Stricter national and local guidelines on opioid prescribing can also be implemented in areas where fatality incidents are particularly high. The regions, such as the US, where opioid-related deaths are still on rise despite the decline in opioid prescribing, other factors that might be contributing to the deaths must also be explored and addressed. Additionally, there should be tighter restrictions on the importation of chemicals at border entries as well as more funding for agents which operate to detect illicit synthesis of fentanyls and dismantle criminal drug networks.¹⁴ The availability of the fentanyl analogues identified in the studies included in this review are often restricted for use in non-humans or only available in specialized settings. For example, carfentanil which was responsible for overdose deaths in our included studies, is only licensed for use in

elephants and other large mammals in the US.⁴⁷ However, illicit manufacturing, import and distribution are key public health concerns. Patients with dual diagnoses of substance misuse and severe mental health are often likely to be at risk of harm from opioid misuse and deaths, and therefore additional consideration are needed from prevention and treatment perspectives.⁴⁸

Conclusion

The steady emergence of novel fentanyl analogues on the illicit drug market poses a global public health threat that is no longer localised to the US. This review shows that the majority of the decedents due to fentanyl analogues associated mortalities were in the United States and were young white males. Approximately, all deaths were unintentional and most used an intravenous route of administration. Novel fentanyl analogues cannot typically be identified using standard analytical methods since they usually have low active concentrations necessitating newer standard testing must be implemented. Overdose due to mixed drug toxicities with other opioids was a major cause of death. Therefore, education for healthcare professionals and patients is required on the appropriate use of prescription opioids and be taught to recognize signs of drug dependence.

Ethical Publication Statement

The authors confirm that they have read the journal's position on issues involved in ethical publication and affirm that this review is consistent with those guidelines.

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