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REVIEW

Causes, Nature and Toxicology of Fentanyl-Associated Deaths: A Systematic Review of Deaths Reported in Peer-Reviewed Literature

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Purpose: Fentanyl poisoning has been widely reported, yet there is a lack of systematic evaluation of the nature and toxicology of associated deaths in the published literature. This article aims to systematically review the nature, causes, routes of administration and toxicology of fentanyl-associated deaths using case studies and case series in peer-reviewed published literature.

Methods: Four electronic databases including Embase, Medline (via Ovid), Scopus and Google Scholar were searched from inception until October 2019 to identify the studies reporting fentanyl related deaths. Two independent reviewers screened and selected the titles and then evaluated the full texts. Only case studies and case series were included. A structured data extraction tool was used to extract data on the number of deaths, routes of administration, concomitant drug use and toxicological data. The Joanna Briggs Institute quality assessment tool was used to evaluate the quality of included studies. Data were synthesized narratively.

Results: Of 1251 articles identified during initial search, 8 case reports and 9 case series met the inclusion criteria. A total of 1969 deaths were reported in the included studies. Deaths were concentrated in the north American region (n = 1946) and the Nordic region (n = 22). Reported causes of death included fentanyl overdose (n = 321, 56.4%), mixed drug toxicity (n = 196, 34.5%), natural (n = 28, 4.9%), other drug toxicity (n = 10, 1.8%), fentanyl and ethanol intoxication (n = 8, 1.4%), incidental (n = 5, <1%) and aspiration (n = 1). Most common routes of use were intravenous (70.5%) and transdermal routes (23.0%). Deaths came swiftly via the intravenous route. Mean level of blood fentanyl amongst all reported deaths was 0.024 µg/mL.

Conclusion: Literature related to fentanyl-associated deaths predominantly come from North America. Deaths are comparatively lower or not reported in peer-reviewed publications from the rest of the world. Abuse through intravenous administration, mixed drug toxicities and self-treatment of breakthrough pain are mainly responsible for majority of the reported deaths.

Keywords: fentanyl, death, nature, cause, toxicology

Introduction

Fentanyl is classified as a schedule 2 controlled drug in the UK and is prescribed for chronic intractable pain.[1] It is a synthetic opioid analgesic and is 50–100 times more potent than its counterpart morphine.[2] This high potency is attributed to its lipophilicity which makes it readily cross the blood brain barrier.[3] Fentanyl has a similar toxicological profile as other opioid analgesics and is associated with side

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effects including respiratory depression, anxiolysis, euphoria, drowsiness, constipation, nausea and cough suppression.[1] Orthostatic hypotension, urinary urgency or retention, postural syncope and chest wall rigidity especially with the intravenous usage are also common.[4]

The opioid crisis in North America has been well recognised and fentanyl remains a key contributor.[5] Cheaper production costs, greater potency and improved side effect profile often leads to fentanyl being favoured over its counterpart morphine. However, prescribing practices are often reported to be sub-optimal.[6] In a Canadian study, approximately three in four fentanyl initiations were deemed to be unsafe due to lack of prior opioid exposure.[6] In 2017 alone, it was estimated that there were 70,000 opiate related deaths in the US.[7,8] Most cases of fentanyl-associated harm, overdose, and death in the US were reported to be related to the illicitly-manufactured fentanyl (IMF).[9] According to the National Forensic Laboratory Information System (NFLIS) reports, there were 4585 confiscations of fentanyl in the year 2014.[10] This data suggests that the rapid increase in fentanyl-associated deaths could be attributed to the increased availability of illegally made, non-pharmaceutical fentanyl and not prescribed fentanyl.[9] This has also given rise to the use of novel opioid derivatives that had emerged in order to circumvent the regulations surrounding novel synthetic opioids (NSOs) such as morphine, heroine and fentanyl.[11]

Since their emergence, NSOs have been associated with severe harm including death.[11] The US Centres for Disease Control and Prevention (CDC) has reported an increase in death associated with opioids (including NSOs) from 9945 deaths in 2016 to 20,145 deaths in 2017.[5] The situation is understood to be similarly concerning in the UK and Europe, however there is a concern in regards to timely availability of toxicological data.[12] Previous systematic reviews on opioids focused on traditional opioids' toxicities and their related mortalities;[13–16] however, none of these reviews highlighted NSOs. This is not surprising as NSOs have only risen to prominence in recent years.[11] Therefore, the present research is imperative as fentanyl contributes to the newest wave of opioid related casualties that is contributing to the larger problem of the opioid epidemic. Whilst there are legal and professional efforts required into combatting this problem, there is a need to identify products implicated, routes of use and toxicological profile in relation to fentanyl-associated deaths. The aim of this study is to systematically review the nature and toxicology of fentanyl-associated deaths using case studies and case series as reported in peer-reviewed published literature.

Methods

This study has been reported based on PRISMA guideline for reporting systematic reviews and meta-analysis. The review was registered on PROSPERO (CRD42020171448).

Data Sources and Searches

Three major online medical databases (Embase, Medline via Ovid and Scopus) and Google Scholar were searched from inception until October 2019. A simple text-based search strategy was used. Search words used were "fentanyl", "deaths" and "case studies" and their synonyms. Reference lists of the included articles were also considered in order to ensure no relevant case studies or case series were missed.

Study Selection

Retrieved articles were imported into RefWorks® where initial screening was carried out. Titles and abstracts were screened against inclusion/exclusion criteria after deduplication. Articles were included if they were case studies and case series that reported deaths of adults (16 years and above) related to fentanyl/NSOs and published in the English language. Articles focusing on the analogues and solely on fentanyl laced products were excluded.

Data Extraction and Quality Assessment

A structured data extraction form was developed and piloted with two included papers and finalised within the research team (see Table 1). In addition to the demographic details of the paper, data on cause of death, dose, and route(s) of administration were extracted by two reviewers independently. The Joanna Briggs Institute (JBI) validated quality assessment tool for case studies and case series was used to assess the quality of included studies. Two authors independently assessed the quality of included studies using the JBI tool.[17] Discrepancies were resolved through discussions and a third reviewer was consulted to resolve disagreements.

Data Synthesis and Analysis

Duplicate, independent extraction of data was undertaken by two reviewers. Where discrepancies occurred, a third reviewer was consulted for a final decision. Owing to the heterogeneity between the included studies in terms of

Table 1 Data Extraction of Included Case Studies and Case Series

Study ID	Country	No. of Fentanyl Death Cases Reported	Study Design	Route of Fentanyl Administration	Cause of Death	Summary of Key Results
Martin et al,[32] 2006	Canada	n = 112 Female: 49 Male: 63	Case series	Oral/Transmucosal: 28 Intravenous: 12 Transdermal: 62 Oral + Transdermal: 6 Inhalation: 1 Transdermal + Intravenous: 2 Unknown: 1	Fentanyl overdose: 54 Mixed drug toxicity: 31 Natural: 11 Fentanyl + ethanol toxicity: 5 Incidental deaths: 5	54 cases in which death was attributed only to fentanyl intoxication with the mean blood concentration of 25 μg/L (range: 3.0–383 μg/L).
Nara et al,[34] 2019	Japan	n = 1 Female Age range: 40–49	Case report	Transdermal	Fentanyl overdose	The measured fentanyl and norfentanyl concentrations in the femoral and cardiac blood were 0.051 and 0.072 μg/mL and 0.033 and 0.076 μg/mL, respectively.
Carson et al,[21] 2010	USA	n = 1 Male Age: 28 White	Case report	Transmucosal (chewing transdermal patch)	Mixed drug toxicity preceding aspiration of transdermal patch	Toxicological analysis of femoral blood reported methamphetamine, fentanyl and norfentanyl concentrations as 1456, 8.6 and 1.4 ng/mL, respectively.
Jumbelic et al,[27] 2010	USA	n = 8 Female: 3 Male: 5	Case reports	Transdermal	Fentanyl overdose	The age range of individuals dying from fentanyl overdose, was from 16 to 49. The blood fentanyl concentrations ranged from 10 to 28 ng/L with an average of 18.3 ng/L.
Edinboro et al,[23] 1997	USA	n = 1 Female Age: 83 White	Case report	Transdermal	Fentanyl overdose	Patient found dead with three 100 mg/h fentanyl patches on her chest. Toxicological analysis produced fentanyl concentrations of blood, 25 ng/mL; brain, 54 ng/g; heart 94 ng/g; kidney 69 ng/g; and liver 104 ng/g.
Henderson et al,[25] 1991	USA	n = 112 Female: 22 (known) Male: 78 (known) Age range: 19–57 White: 50 (known) Black: 20 (known) Hispanic: 29 (known) Asian: 1 (known)	Case series	Intravenous: 71 Unknown: 4 37 autopsy reports unavailable so route for these patients unknown	Fentanyl overdose	Mean fentanyl concentrations in the body fluids were quite low: 3.0 ± 3.1 ng/mL (0.3 ± 0.31 micrograms/dL) in blood and 3.9 ± 4.3 ng/mL (0.39 ± 0.43 micrograms/dL) in urine, measured by radioimmunoassay.

(*Continued*)

Table 1 (Continued).

Study ID	Country	No. of Fentanyl Death Cases Reported	Study Design	Route of Fentanyl Administration	Cause of Death	Summary of Key Results
Geile et al,[24] 2019	Germany	n = 11 Female: 6 Male: 5 Age range: 17–95	Case series	Transdermal: 11	Mixed drug toxicity: 5 Fentanyl overdose: 1 Natural: 5	Between one and three patches were applied (mean 1.7 patches) with a dose ranging between 25 and 300mg/h (mean 97.7mg/h). Fentanyl could be quantified in nine cases with concentrations ranging between 0.8 and 29.3 ng/mL (mean 11.9 ng/mL). Norfentanyl could be quantified in five cases with concentrations ranging between 2.3 and 823 ng/mL (mean 234.5 ng/mL).
Tharp et al,[35] 2004	USA	n = 4 Male: 4 Age range: 35–42	Case reports	Intravenous: 4 (extraction of API from transdermal patches)	Fentanyl overdose: 4	All reported deaths were attributed to fentanyl intoxication, with blood concentrations ranging from 5 to 27 μg/L.
Algren et al,[20] 2013	USA	n = 101 Female: 39 Male: 62 Age range: 18–60 White: 58 Black: 41 Hispanic: 1 Unknown: 1	Case series	Intravenous (specific numbers unclear)	Fentanyl overdose Mixed drug toxicity Specific numbers unclear	A significant interaction occurred between gender and age, and gender and marital status. Median fentanyl concentration in central blood samples was 0.02 μg/mL (*n* = 91, range <0.002–0.051 μg/mL) and 0.02 μg/mL (*n* = 32, range <0.004–0.069 μg/mL) in peripheral blood samples.
Lee et al,[30] 2016	USA	n = 72 Female: 21 Male: 51 Age range: 19–78 White: 67 Black: 4 Hispanic: 1	Case series	Unreported	Fentanyl overdose: 40 Mixed drug toxicity: 22 Natural: 10	Fentanyl concentrations ranged from 2.5 to 68 ng/mL (n = 66; median: 9.8 ng/mL). Most of the cases (85%) had indications of possible drug abuse with heroin use being the most often suspected.
Lilleng et al,[31] 2004	Norway	n = 2 Male: 2 Age range: 41–42	Case reports	Intravenous: 4 (extraction of API from transdermal patches)	Fentanyl overdose: 1 Mixed drug toxicity: 1	In the first case, the toxicological analysis revealed fentanyl (2.7 ng/mL), morphine (31.4 ng/mL), and ethanol (1.1 g/L) in post-mortem blood. In the second case, the analysis revealed fentanyl (13.8 ng/mL), 7-aminoclonazepam (57.1 ng/mL), and sertralin (91.9 ng/mL) in post-mortem blood and a small amount of ethanol (0.1 g/L) in post-mortem urine.

(*Continued*)

Table 1 (Continued).

Study ID	Country	No. of Fentanyl Death Cases Reported	Study Design	Route of Fentanyl Administration	Cause of Death	Summary of Key Results
Denton et al,[22] 2008	USA	n = 350 Female: 55 Male: 295 Age range: 17–68 White: 142 Black 258	Case series	Intravenous: 350	Fentanyl overdose: 175 Mixed drug toxicity: 77 Unknown: 98	The average concentration of fentanyl in all fatalities in post-mortem peripheral blood was 22.8 ng /mL (median 16.6; range 0.8–164). most deaths were fentanyl intoxication without other drugs or alcohol (50%), followed by fentanyl and cocaine intoxication (22%).
Jones et al,[26] 2008	USA	n = 1013 Female: 196 (known) Male: 788 (known) Ages: 577 between 35–54 White: 545 (known) Black: 392 (known) Hispanic: 41 (known)	Case series	Intravenous (specific numbers unclear)	Fentanyl overdose and mixed drug toxicity (specific numbers not reported)	Most of the implicated Non-manufactured fentanyl was mixed with heroin or cocaine.
Kronstrand et al,[29] 1997	Sweden	n = 9 Male: 9 Age range: 22–44 White: 9	Case reports	Intravenous	Fentanyl overdose: 7 Natural: 1 Unknown: 1	Fentanyl concentrations ranged from 0.5 to 17 ng g-1 blood, and from 5 to 160 ng mL-1 urine. Other drugs found were amphetamine, ethanol and benzodiazepines. Morphine was found in one case only.
Mercado et al,[33] 2014	USA	n = 69 Female: 21 Male: 42 Unknown: 6 Age range: 17–65 White: 61 Black: 3 Hispanic: 4 Other: 1	Case series	Intravenous (specific numbers not reported)	Fentanyl overdose and mixed drug toxicity (specific numbers not reported)	Illicit-fentanyl decedents were younger than other drug decedents ($P = 0.005$). When compared to other drug decedents, illicit fentanyl decedents were reported to be significant recent users of other type of illicit drugs (62.3% vs 45.6%, $P = 0.002$), and specifically heroin (49.3% vs 28.3%, $P = 0.000$).
Woodall et al,[36] 2008	USA	n = 7 Female: 3 Male: 4 Ages: 20–51	Case reports	Transdermal	Fentanyl overdose: 2 Fentanyl + ethanol toxicity: 3 Mixed drug toxicity: 1 Natural: 1	In four of the seven cases the decedents had their own prescription for fentanyl, although each of these individuals was also known to have a history of drug abuse. Post-mortem blood fentanyl concentrations were determined in all cases and ranged from 7 to 97 ng /mL.

(*Continued*)

Table 1 (Continued).

Study ID	Country	No. of Fentanyl Death Cases Reported	Study Design	Route of Fentanyl Administration	Cause of Death	Summary of Key Results
Krinsky et al,[28] 2011	Mexico	n = 96 Female: 50 Male: 46 Age range: 18–89 White non-Hispanic: 82 White Hispanic: 8 Native American: 5 Black: 1	Case series	Transdermal: 58 Ingestion: 4 Intravenous: 5 Unknown: 30	Fentanyl overdose: 27 Mixed drug toxicity: 59 Other drug overdose: 10	The mean fentanyl concentration in females was 22.8 (SD, 49.4) ng/mL, with a median of 13 ng/mL and a range of 2 to 400 ng/mL. In males, the mean was 18.7 (SD, 27.1) ng/mL, with a median of 11 ng/mL and a range of 0.5 to 150 ng/mL. For overdose deaths, the mean fentanyl concentration in females was 27.1 (SD, 58.9) ng/mL, with a median of 14 ng/mL and a range of 3 to 400 ng/mL. In males, the mean was 16.2 (SD, 13.2) ng/mL, with a median of 14 ng/mL and a range of 0.5 to 50 ng/mL

different study designs and outcomes assessed, narrative synthesis was conducted. The data was presented according to the Synthesis Without Meta-analysis (SWiM) guideline[18] and recommendations in the 2019 Cochrane Handbook for Systematic Reviews of Interventions where applicable.[19] The narrative synthesis of the collected data was undertaken considering the geographical distribution, causes, nature, and toxicology of fentanyl-associated deaths. All data in the narrative synthesis was presented in tables of frequencies and percentages except for the toxicology data that was be presented as mean and range values.

Results

A total of 1226 records were screened of which 17 studies were included (Figure 1).[20–36] Of the 17 included articles, eight were case reports and nine were case series (see Table 1). The quality of reporting of included case studies was generally good. Demographic characteristics, patient history, clinical presentation, adverse events and take away lessons were clearly provided in most articles. Patient history, however, was either unclear or not reported in only three (37.5%) of eight articles. The quality of case series was variable with a lack of clear inclusion criteria and analyses plans (Tables 2 and 3).

Demography

A total of 1969 deaths were reported in included studies. Most deaths occurred in North America with United States reporting the highest number of deaths (n= 1738), followed by Canada (n=112) and Mexico (n=96). Outside North America, deaths were reported in Western Europe including Germany (n=11) and Nordic regions including Sweden (n=9) and Norway (n=9) (Table 1). Recent cases were identified from Far East Asia, Japan (n=1). The study conducted by Nara et al, was the first forensic autopsy report to be undertaken in Japan.[34] Where ethnicity was reported, most of the deaths were reported among whites 1024 (56.1%) followed by blacks 719 (39.38%) and Hispanics 77 (4.22%). The majority of the patients who were reported dead were males 1456 (75.83%).

Routes of Administration

The route of administration of fentanyl was reported in 645 cases of deaths. The most common route of administration was intravenous (n = 455, 70.5%), followed by application of transdermal fentanyl patches (n = 148, n = 23.0%). Other less common routes of administration reported were oral/transmucosal (n = 29, 4.5%), oral and transdermal usage simultaneously (n = 6, <1%), ingestion (n = 4 <1%), transdermal and intravenous route simultaneously (n = 2, <1%) and inhalation (n = 1, <1%).

Cause of Deaths

Causes of deaths were not reported for all the deaths reported in included studies. Reported causes of death were: fentanyl overdose (n = 321, 56.4%), mixed drug toxicity (n = 196, 34.5%), natural (n = 28, 4.9%), other drug toxicity (n = 10, 1.8%), fentanyl and ethanol

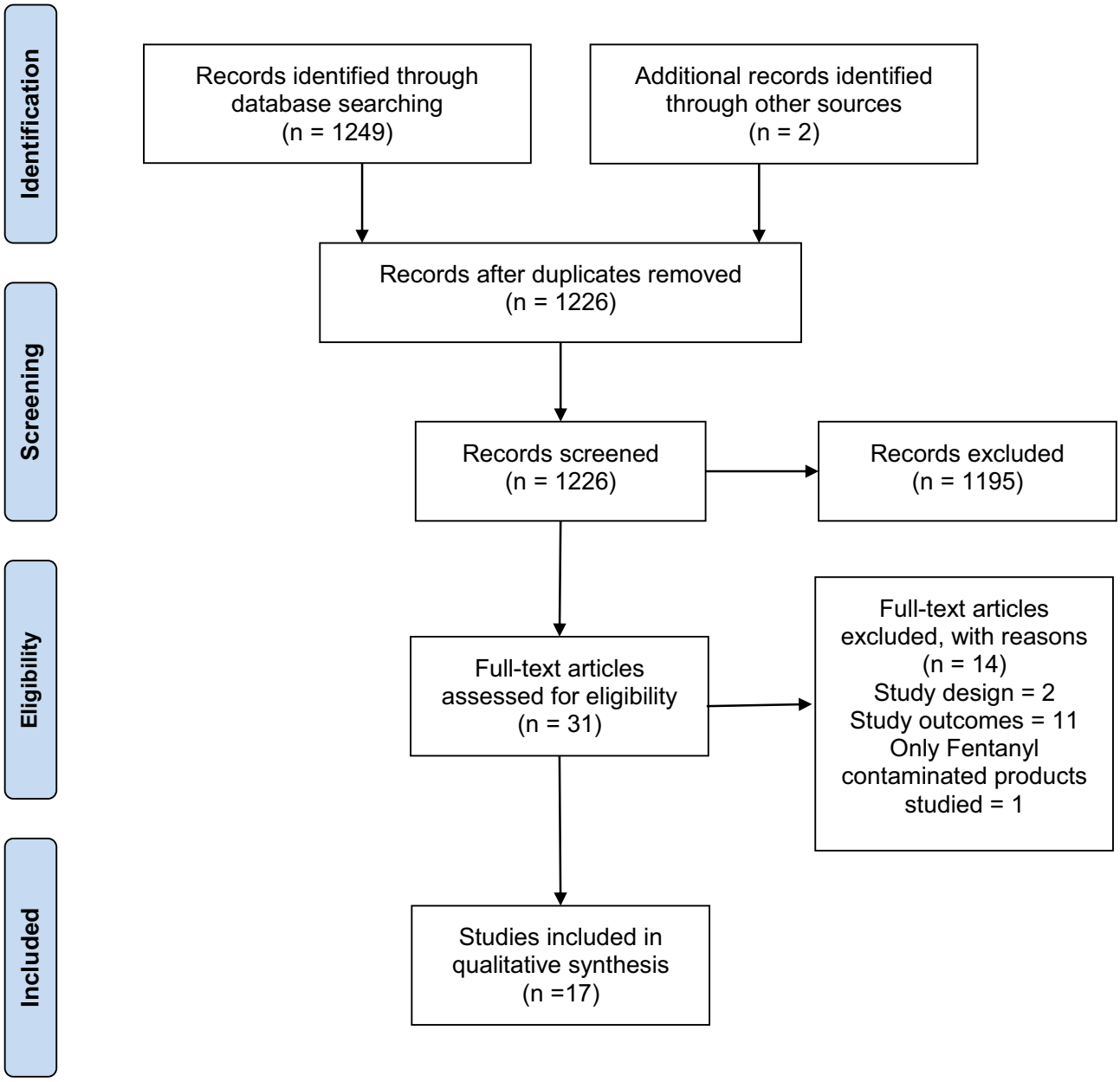

Figure 1 PRISMA flow diagram.
Note: PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of clinical epidemiology.* 2009;62(10). Creative Commons.[37]

intoxication (n = 8, 1.4%), incidental (n = 5, <1%), and aspiration (n = 1). Among mixed drug toxicities, the most common concomitant drugs were other opioid type drugs, cocaine, benzodiazepines, sedating antihistamines and a wide array of antidepressants (Table 4). Diphenhydramine was the most common sedating antihistamine detected in those who died due to mixed drug toxicities. Among the drugs commonly abused together with fentanyl, there were a total of 28 drugs that had the potential for serotonin syndrome. For the purpose of this research, fentanyl and alcohol mixed toxicity were considered separately to mixed drug toxicity. Other uncommon causes of death included natural deaths, where fentanyl was detected by toxicology, but the patient died of natural causes. Incidental deaths, where fentanyl was detected by toxicology, but the patient died via accidents or injuries such as hanging or gunshot wounds. Some anomalous causes of death were also reported. A case study related to a patient chewing on a transdermal patch to obtain drug via a transmucosal route.[21] Whilst chewing the patch, the

Table 2 Quality Assessment of Included Case Studies

	Nara et al,[34] 2019	Carson et al,[21] 2010	Jumbelic et al,[27] 2010	Edinboro et al,[23] 1997	Tharp et al,[35] 2004	Lilleng et al,[31] 2004	Kronstrand et al,[29] 1997	Woodall et al,[36] 2008
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
Was the post-intervention clinical condition clearly described?	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**	
✓	✖			-			N/A	

fentanyl patch fell into his throat and the patient lacked capacity to react due to the sedative effect of the drug. Subsequently, the patient died of asphyxiation. Whilst this cause of death is not readily associated with any dosage forms of fentanyl, the events leading to the patient's death were directly caused by the drug.

Nature of Deaths

Given the data reported in the included studies, the precise nature of fentanyl-associated deaths remained unclear. It was also very difficult to ascertain whether patients were prescribed fentanyl legitimately, as the statistics were not reported in most of the included studies. One study conducted by Jumbelic (2010) reported that five out of eight (62.5%) of fentanyl-associated death cases included in this case study were legitimately prescribed.[27]

Toxicology

Blood toxicology reports of patients with fentanyl-associated patient deaths were reported in only 12 studies. There was a great variation in the concentration of fentanyl reported in blood toxicological reports. The mean fentanyl concentration in blood from all deaths (reported in 12 of 17 articles) was 0.024 µg/mL (range 0.0002–0.38 µg/mL).

Some evidence suggested that the variability in fentanyl blood concentrations was dependent on the site where blood was drawn.[32,34] Nara et al[34] reported the case of a lady who died of a fentanyl overdose via the transdermal route of administration. The fentanyl concentration at the femoral and cardiac sites were 0.051 µg/mL and 0.033 µg/mL respectively. When examining toxicology post-mortem, researchers in the study took blood samples from different locations. These locations included femoral, cardiac, subclavian and iliac arteries (Table 5).

Deaths reported due to mixed drug toxicity had the highest mean fentanyl concentration at 0.034 µg/mL (range 0.0027–0.12 µg/mL) followed by fentanyl intoxication and fentanyl plus ethanol toxicity with 0.017µg/mL (range 0.002–0.38 µg/mL) and 0.015µg/mL (range 0.0064–0.037 µg/mL) respectively. The greatest concentration observed

Table 3 Quality Assessment of Included Case Series

	Martin et al,[32] 2006	Henderson et al,[25] 1991	Geile et al,[24] 2019	Algren et al,[20] 2013	Lee et al,[30] 2016	Denton et al,[22] 2008	Jones et al,[26] 2008	Mercado et al,[33] 2014	Krinsky et al,[28] 2011
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	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?	–	–	–	✓	–	–	–	✓	–

was from intravenous injection at 0.383 µg/mL. Martin et al reported that this death was as a result of an individual injecting the contents of five transdermal patches.[32] This reflected the extremely high mortality of injecting the contents of patches. A transmucosal route resulted in the lowest fentanyl concentration with a mean (range) of 0.0086 µg/mL. Those who had ingested fentanyl had the highest mean (range) blood concentration post-mortem with 0.028 (0.007–0.097) µg/mL. This was not anticipated given that fentanyl passing through the stomach will be greatly metabolised. Transdermal administration resulted in mean (range) concentration of 0.019 (0.0008–0.097) µg/mL. The mean (range) concentration of fentanyl without the use of other drugs was 0.025 0.005–0.027) µg/mL. When concomitant drugs were present, the mean (range) blood concentration were 0.017 (0.005–0.051) µg/mL. As aforementioned, this could have resulted from an increased tolerance to the opioid from chronic drug abuse. The full details of this case are however unknown. Of the 17 articles included in this systematic review only one study reported non measurable fentanyl concentration in blood.[24] Three studies reported norfentanyl concentrations.[21,25,34] Norfentanyl is one of the main metabolites of fentanyl that is produced by oxidative N-dealkylation.[34]

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

Drug Class	Drug	Total Number Reported in Toxicology	% of the Total Fentanyl-Associated Deaths Reported in the Included Studies (n=1969)
Opiates	Morphine (n = 258) Methadone (n = 84) Codeine (n = 87) Hydrocodone (n = 13) Oxycodone (n = 93) Heroin (n = 190) Tapentadol (n = 1) Piritramide (n = 1) Propoxyphene (n = 2) Hydromorphone (n = 2) Pethidine (n = 3)	734	37%
Benzodiazepine*	Diazepam Alprazolam Chlordiazepoxide Clonazepam	285	14%
Antidepressant/Antipsychotic*	Citalopram (n = 10) Amitriptyline (n = 6) Doxepin (n = 2) Mirtazapine (n = 1) Sertraline (n = 5) Paroxetine (n = 3) Quetiapine (n = 1) Trazodone (n = 2) Fluoxetine (n = 5) Norfluoxetine (n = 5) Nortriptyline (n = 8) Olanzapine (n = 2) Lithium (n = 1) Venlafaxine (n = 2) Chlorpromazine (n = 3)	122	17%
Hypnotic/Tranquiliser	Zolpidem (n = 18) Zopiclone (n = 3) Meprobamate (n = 1) Carisoprodol (n = 14)	36	1.8%
Sedating Antihistamines	Diphenhydramine (n = 17) Promethazine (n = 2)	19	0.9%
	Cocaine	295	15%
Antihypertensive	Bisoprolol (n = 2) Metoprolol (n = 4) Amlodipine (n = 2) Candesartan (n = 1) Valsartan (n = 1) Furosemide (n = 1)	11	0.5%
	Methamphetamine	17	0.8%
Antiepileptic	Carbamazepine (n = 1) Gabapentin (n = 1)	2	0.1%

Notes: *Precise figures for benzodiazepine drugs not recorded as some case series recorded benzodiazepines as their own standalone category. Similarly, antidepressants/antipsychotic drugs were only recorded in some case studies and case series. Additional deaths by these drugs were stated as standalone figures and added to the final total.

Table 5 Data Extraction of Toxicology from Included Case Studies

Study ID	Patient Demographic (Gender, Age)	Route of Administration	Cause of Death	Fentanyl Concentration (μg/mL) from Specified Blood Source	Evidence of Concomitant Drugs
Nara et al,[34] 2019	Female, 40–49	Transdermal	Fentanyl Overdose	Femoral: 0.051 Cardiac: 0.033	Yes
Jumbelic et al,[27] 2010	Female 43	Transdermal	Fentanyl Overdose	Subclavian: 0.022	Yes
Jumbelic et al,[27] 2010	Male 49	Transdermal	Fentanyl Overdose	Femoral: 0.022	Yes
Jumbelic et al,[27] 2010	Male 28	Transdermal	Fentanyl Overdose	Subclavian: 0.028	Yes
Jumbelic et al,[27] 2010	Male 16	Transdermal	Fentanyl Overdose	Iliac: 0.005	Yes
Jumbelic et al,[27] 2010	Female 49	Transdermal	Fentanyl Overdose	Subclavian: 0.01	Yes
Jumbelic et al,[27] 2010	Male 37	Transdermal	Fentanyl Overdose	Femoral: 0.013	Yes
Jumbelic et al,[27] 2010	Male 18	Transdermal	Fentanyl Overdose	Cardiac: 0.014	Yes
Jumbelic et al,[27] 2010	Female 43	Transdermal	Fentanyl Overdose	Iliac: 0.019	Yes
Edinboro et al,[23] 1997	Female 83	Transdermal	Fentanyl Overdose	Source not specified: 0.025	No
Tharp et al,[35] 2004	Male 35	Intravenous	Fentanyl Overdose	Source not specified: 0.005–0.027	No
Tharp et al,[35] 2004	Male 38	Intravenous	Fentanyl Overdose	Source not specified: 0.005–0.027	No
Tharp et al,[35] 2004	Male 42	Intravenous	Fentanyl Overdose	Source not specified: 0.005–0.027	Yes
Tharp et al,[35] 2004	Male 39	Intravenous	Fentanyl Overdose	Source not specified: 0.005–0.027	Yes
Lilleng et al,[31] 2004	Male 41–42	Intravenous	Mixed Drug Toxicity	Source not specified: 0.0027	Yes
Lilleng et al,[31] 2004	Male 41–42	Intravenous	Fentanyl Overdose	Source not specified: 0.0138	Yes
Kronstrand et al,[29] 1997	Male 29	Intravenous	Fentanyl Overdose	Femoral: 0.004	Yes
Kronstrand et al,[29] 1997	Male 22	Intravenous	Fentanyl Overdose	Femoral: 0.005	Yes
Kronstrand et al,[29] 1997	Male 40	Intravenous	Fentanyl Overdose	Femoral: 0.017	Yes
Kronstrand et al,[29] 1997	Male 44	Intravenous	Fentanyl Overdose	Femoral: 0.005	Yes
Kronstrand et al,[29] 1997	Male 42	Intravenous	Fentanyl Overdose	Femoral: 0.006	Yes
Kronstrand et al,[29] 1997	Male 42	Intravenous	Fentanyl Overdose	Femoral: 0.009	Yes
Kronstrand et al,[29] 1997	Male 26	Intravenous	Fentanyl Overdose	Femoral: 0.002	Yes
Woodall et al,[36] 2008	Male 42	Transdermal	Fentanyl Overdose	Cardiac: 0.022	Yes
Woodall et al,[36] 2008	Female 20	Transdermal	Fentanyl Overdose	Femoral: 0.013	Yes
Woodall et al,[36] 2008	Female 51	Transdermal	Mixed Drug Toxicity	Femoral: 0.097	Yes
Woodall et al,[36] 2008	Female 42	Transdermal	Fentanyl + Ethanol Toxicity	Femoral: 0.028 Cardiac: 0.032	Yes
Woodall et al,[36] 2008	Male 32	Transdermal	Fentanyl + Ethanol Toxicity	Cardiac 0.007	Yes
Woodall et al,[36] 2008	Male 41	Transdermal	Fentanyl + Ethanol Toxicity	Cardiac: 0.008	Yes
Carson et al,[21] 2010	Male 28	Transmucosal	Mixed Drug Toxicity (Preceding Aspiration)	Femoral: 0.0086	Yes

Discussion

This is the first study to systematically review case studies and case series related to the deaths attributed to fentanyl. This report has reinforced the dangers of administering fentanyl via all routes especially IV and transdermal routes. Multiple fentanyl-associated deaths were recorded in not only North America but also in Europe and Asia. The majority of the deaths included in this review were attributed to intravenous route. An intravenous route provides the quickest onset of action completely bypassing the blood brain barrier. Jansen pharmaceuticals has also stated in its product literature that fentanyl is more likely to cause chest wall rigidity when used intravenously.[4] This fact could have contributed to the respiratory depression and subsequent death of victims.

The transmucosal route was associated with the lowest fentanyl concentration, however this is not a representative result as firstly, there was only a single death via the transmucosal route that included toxicological data. Secondly, the reported patient died of aspiration thus it is unlikely that the value observed had lethal effects. It would be expected that the transmucosal route would result in greater concentration than observed and produce greater blood concentration than the orally ingested route.[37]

There seemed to be no clear correlation between the post-mortem blood samples of fentanyl and routes of administration or cause of death. Therefore, many factors must be considered when researching toxicology including route of administration, concomitant drug use and opioid

naivety. Using an intravenous route of administration is anticipated to produce lesser blood fentanyl concentrations given its high lipophilicity and uptake into tissues. Transdermal administration would be expected to produce the greatest blood fentanyl concentrations due to its prolonged release mechanism.[32]

A common theme that recurred in transdermal associated deaths was the patient's lack of understanding of their prescription medication. Patients using multiple fentanyl patches to treat their breakthrough pain led to several deaths. Explicit education is needed for those patients to prevent such deaths occurring in the future. Furthermore, patients who died because of fentanyl transdermal patches often found ways to extract the active pharmaceutical ingredient from transdermal patches to inject intravenously. Fentanyl patches (Duragesic®) follow a reservoir drug delivery design in which the drug is held within the centre of the patch encased by a backing layer and rate controlling membrane which is in contact with the skin.[38] By disturbing the integrity of the rate controlling membrane and/or backing layer, drug from the reservoir can be extracted.

Simultaneous drug usage was extremely common in the case studies and case series reviewed.

The most common concomitant drug classes reported were other opiates (n = 734), cocaine (n = 295), benzodiazepines (n = 285) and antidepressants (n = 122). Whilst this was not investigated in this review, the possibility of death caused by serotonin syndrome cannot be ignored. The risk of serotonin syndrome is comparatively small with intravenous fentanyl as this opioid has a small half-life however when used as a prolonged release transdermal formulation the risk is greatly increased. The study has also implied that the most at-risk patients are those with histories of chronic drug abuse and those where polypharmacy is common. Antidepressants are also unsurprisingly common as polypharmacy is rife in those with severe pain and/or cancer, for which fentanyl is usually prescribed. The effects of using different opioids alongside fentanyl will inevitably be additive and enhance the central nervous system (CNS) effects of the drugs. In a similar way, the administration of antidepressants, drugs which are known to cause anticholinergic blockade, will also add to the sedating and CNS depressive effects of fentanyl.

Limitations

This study has some limitations. The quality of case studies and case series included in this article are variable and results should therefore be interpreted with caution. The opioid epidemic is a large-scale problem involving several synthetic opioids and only one of which was investigated here. Also, fentanyl itself has many different analogues of varying potency which were not investigated in this review. The study population of this review was only restricted to the adult population. Children have been reported to have died via fentanyl exposure in some studies.[39,40] Studies that were published in non-indexed journals and unpublished reports were also not included in this review which could have proved valuable sources of information.

Implications for Practice and Research

This report highlights the need to carefully review the prescribing of fentanyl, particularly in those areas where there are extremely high instances of death, eg, in North America. It should be ensured that the drug is only prescribed for those who absolutely require it and in accordance with professional guidelines. All healthcare professionals must provide explicit and clear education to those taking fentanyl with regards to how the drug should be used appropriately and the consequences of overuse, misuse and diversion. Prescribers may consider providing naloxone to said patients as symptoms may take hold too quickly for emergency services to arrive. This could potentially save lives. A patient's tolerance to opioids also affects the threshold to which fentanyl becomes toxic. Those patients who do not receive chronic opioid treatment are said to be opioid naïve and are anticipated to have lower blood fentanyl levels upon death.

This review has established that chronic drug addicts have greater tendencies to misuse the drug. These patients need to be informed about the signs and symptoms of respiratory depression and chest wall rigidity. This will enable them to respond to these signs in a rapid manner, alerting emergency services and preventing loss of life. There is a need to improve access to preventative services including the drug and alcohol services and provision of naloxone to the vulnerable patient populations such as homeless populations who have high prevalence of opioid misuse and also demonstrate dual diagnoses of opioid misuse and severe mental health.[41–43] Key stakeholders should focus on raising public awareness of fentanyl and its dangers when misused.

Conclusion

Deaths due to fentanyl as reported in the published studies is concentrated in North America. Deaths are comparatively lower or not reported in peer-reviewed publications in the rest of the world. Abuse through intravenous administration, mixed drug toxicities including other opiates and antidepressants, and self-treatment of breakthrough pain are mainly responsible for most of the deaths. There is a need for wider regulatory measures, education of healthcare professionals and patients in combating the problem.

Ethics Statement

This review did not require ethical approval.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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References

1. National Institute of Clinical Excellence. FENTANYL | drug | BNF content published by NICE; 2019. Available from: https://bnf.nice.org.uk/drug/fentanyl.html. Accessed September 02, 2020.
2. Volpe D, Tobin G, Mellon R, et al. Uniform assessment and ranking of opioid Mu receptor binding constants for selected opioid drugs. *Regulatory Toxicol Pharmacol*. 2011;59(3):385–390. doi:10.1016/j.yrtph.2010.12.007
3. Hug C, Murphy M. Fentanyl Disposition in Cerebrospinal Fluid and Plasma and Its Relationship to Ventilatory Depression in the Dog. *Anesthesiology*. 1979;50(4):342–349. doi:10.1097/00000542-197904000-00011
4. Çoruh B, Tonelli M, Park D. Fentanyl-Induced Chest Wall Rigidity. *Chest*. 2013;143(4):1145–1146. doi:10.1378/chest.12-2131
5. National Institute on Drug Abuse. Opioid Overdose Crisis. Available from: https://www.drugabuse.gov/drug-topics/opioids/opioid-overdose-crisis. Accessed September 02, 2020.
6. Friesen K, Woelk C, Bugden S. Safety of fentanyl initiation according to past opioid exposure among patients newly prescribed fentanyl patches. *Can Med Assoc J*. 2016;188(9):648–653. doi:10.1503/cmaj.150961
7. U.S Centers for Disease Control and Prevention, National Center for Health Statistics. New Data Show Growing Complexity of Drug Overdose Deaths in America. 2018. Available from https://www.cdc.gov/media/releases/2018/p1221-complexity-drug-overdose.html. Accessed September 02, 2020.
8. U.S. Centers for Disease Control and Prevention. Drug and Opioid-Involved Overdose Deaths — united States, 2013-2017; 2019. Available from https://www.cdc.gov/mmwr/volumes/67/wr/mm675152e1.htm. Accessed September 02, 2020..
9. U.S. Centers for Disease Control and Prevention. What is Fentanyl? 2020. Available from https://www.cdc.gov/drugoverdose/opioids/fentanyl.html. Accessed October 25, 2020.
10. Centers for Disease Control and Prevention. *CDC Health Advisory: Increases in Fentanyl Drug Confiscations and Fentanyl-Related Overdose Fatalities*. HAN Health Advisory; 2015.
11. United Nations Office On Drugs and Crime. Global Synthetic Drugs Assessment. UNODC; Vienna, Austria: 2017. Available from: http://www.unodc.org/documents/scientific/Global_Drugs_Assessment_2017.pdf. Accessed September 03, 2020.
12. National Crime Agency. Recent Deaths Possibly Linked to Fentanyl. London: NCA; 2017. Available from: https://www.nationalcrimeagency.gov.uk/who-we-are/publications/7-recent-deaths-possibly-linked-to-fentanyl/file. Accessed September 03, 2020.
13. King NB, Fraser V, Boikos C, Richardson R, Harper S. Determinants of increased opioid-related mortality in the United States and Canada, 1990–2013: a systematic review. *Am J Public Health*. 2014;104(8):e32. doi:10.2105/AJPH.2014.301966
14. Degenhardt L, Bucello C, Mathers B, et al. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. *Addiction*. 2011;106(1):32–51. doi:10.1111/j.1360-0443.2010.03140.x
15. Sordo L, Barrio G, Bravo MJ, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ*. 2017;26:357.
16. Edwards ES. Patient characteristics and outcomes in unintentional, non-fatal prescription opioid overdoses: a systematic review. *Pain Physician*. 2016;19:215–228.
17. Joanna Briggs Institute. Critical appraisal tools. Available from: https://joannabriggs.org/critical-appraisal-tools. Accessed February 02, 2020.
18. Campbell M, McKenzie JE, Sowden A, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ*. 2020;368:l6890. doi:10.1136/bmj.l6890
19. Higgins JPT, Thomas J, Chandler J, et al., editors. *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd ed. Chichester (UK): John Wiley & Sons; 2019.
20. Algren D, Monteilh C, Punja M, et al. Fentanyl-associated Fatalities Among Illicit Drug Users in Wayne County, Michigan (July 2005–May 2006). *J Med Toxicol*. 2013;9(1):106–115. doi:10.1007/s13181-012-0285-4
21. Carson H, Knight L, Dudley M, Garg U. A fatality involving an unusual route of fentanyl delivery: chewing and aspirating the transdermal patch. *Leg Med*. 2010;12(3):157–159. doi:10.1016/j.legalmed.2010.03.001
22. Denton J, Donoghue E, McReynolds J, Kalelkar M. An Epidemic of Illicit Fentanyl Deaths in Cook County, Illinois: september 2005 through April 2007. *J Forensic Sci*. 2008;53(2):452–454. doi:10.1111/j.1556-4029.2008.00669.x
23. Edinboro L, Poklis A, Trautman D, Lowry S, Backer R, Harvey C. Fatal Fentanyl Intoxication Following Excessive Transdermal Application. *J Forensic Sci*. 1997;42(4):14196J. doi:10.1520/JFS14196J
24. Geile J, Maas A, Kraemer M, Doberentz E, Madea B. Fatal misuse of transdermal fentanyl patches. *Forensic Sci Int*. 2019;302:109858. doi:10.1016/j.forsciint.2019.06.016
25. Fentanyl-Related Deaths: HG, Demographics C. Toxicology of 112 Cases. *J Forensic Sci*. 1991;36(2):13045J.

26. Jones TS, Krzywicki L, Maginnis J, et al. Nonpharmaceutical fentanyl-related deaths-multiple states, April 2005-March 2007 (Reprinted MMWR, vol 57, pg 793-796, 2008). *JAMA*. 2008;300(13):1512–1513.
27. Jumbelic MI. Deaths With Transdermal Fentanyl Patches. *Am J Forensic Med Pathol*. 2010;31(1):18–21. doi:10.1097/PAF.0b013e31818738b8
28. Krinsky C, Lathrop S, Crossey M, Baker G, Zumwalt R. A Toxicology-Based Review of Fentanyl-Related Deaths in New Mexico (1986–2007). *Am J Forensic Med Pathol*. 2011;32(4):347–351. doi:10.1097/PAF.0b013e31822ad269
29. Kronstrand R, Druid H, Holmgren P, Rajs J. A cluster of fentanyl-related deaths among drug addicts in Sweden. *Forensic Sci Int*. 1997;88(3):185–195. doi:10.1016/S0379-0738(97)00068-6
30. Lee D, Chronister C, Broussard W, et al. Illicit Fentanyl-Related Fatalities in Florida: toxicological Findings. *J Anal Toxicol*. 2016;40(8):588–594. doi:10.1093/jat/bkw087
31. Lilleng P, Mehlum L, Bachs L, Morild I. Deaths After Intravenous Misuse of Transdermal Fentanyl. *J Forensic Sci*. 2004;49(6):1–3.
32. Martin T, Woodall K, McLellan BA. Fentanyl-Related Deaths in Ontario, Canada: toxicological Findings and Circumstances of Death in 112 Cases (2002-2004). *J Anal Toxicol*. 2006;30(8):603–610. doi:10.1093/jat/30.8.603
33. Mercado M, Sumner S, Spelke M, Bohm M, Sugerman D, Stanley C. Increase in Drug Overdose Deaths Involving Fentanyl—Rhode Island, January 2012–March 2014. *Pain Medicine*. 2018;19(3):511–523. doi:10.1093/pm/pnx015
34. Nara A, Yamada C, Saka K, et al. A Fatal Case of Poisoning with Fentanyl Transdermal Patches in Japan. *J Forensic Sci*. 2019;64(6):1936–1942.
35. Tharp A, Winecker R, Winston D. Fatal Intravenous Fentanyl Abuse. *Am J Forensic Med Pathol*. 2004;25(2):178–181. doi:10.1097/01.paf.0000127398.67081.11
36. Woodall K, Martin T, McLellan B. Oral Abuse of Fentanyl Patches (Duragesic®): seven Case Reports. *J Forensic Sci*. 2008;53(1):222–225. doi:10.1111/j.1556-4029.2007.00597.x
37. 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)
38. Streisand J, Ashburn M, LeMaire L, Varvel J, Stanley T, Tarver S. Bioavailability and absorption of oral transmucosal fentanyl citrate. *Anesthesiology*. 1989;71(Supplement):A230. doi:10.1097/00000542-198909001-00230
39. Taghizadeh SM, Soroushnia A, Mohamadnia F. Preparation and in vitro evaluation of a new fentanyl patch based on functional and non-functional pressure sensitive adhesives. *AAPS PharmSciTech*. 2010;11(1):278–284. doi:10.1208/s12249-009-9366-3
40. Teske J, Weller J, Larsch K, Troger H, Karst M. Fatal outcome in a child after ingestion of a transdermal fentanyl patch. *Int J Legal Med*. 2007;121(2):147–151. doi:10.1007/s00414-006-0137-3
41. Bakovic M, Nestic M, Mayer D. Death by band-aid: fatal misuse of transdermal fentanyl patch. *Int J Legal Med*. 2015;129(6):1247–1252.
42. Bowen M, Marwick S, Marshall T, et al. Multi-morbidity and emergency department visits by a homeless population: a database study in specialist general practice. *Br J General Practice*. 2019;69(685):e515.
43. Gunner E, Chandan SK, Marwick S, et al. Provision and accessibility of primary healthcare services for people who are homeless: a qualitative study of patient perspectives in the UK. *Br J General Practice*. 2019;69(685):e526. doi:10.3399/bjgp19X704633
44. Gibson Smith K, Paudyal V, MacLure K, et al. Relocating patients from a specialist homeless healthcare centre to general practices: a multi-perspective study. *Br J General Practice*. 2018;68(667):e105–e113. doi:10.3399/bjgp18X694577