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REVIEW

Does occupational exposure to fentanyl cause illness? A systematic review

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ABSTRACT

Introduction: The opioid epidemic in the United States continues to result in an increasing number of deaths and is increasingly dominated by fentanyl and fentanyl analogs. As a result, first responders are likely to come into contact with fentanyl-containing substances daily. Concerns persist regarding occupational exposure resulting in intoxication. We performed a systematic review to describe occupational illnesses from fentanyl and its analogs.

Methods: We conducted a systematic review of the literature following the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to assess the danger of occupational exposure to fentanyl. The PubMed, EMBASE, Google Scholar, SCOPUS, CINAHL, and National Institute for Occupational Safety and Health databases were queried to identify occupational fentanyl exposures. Studies included were single case reports, case series, observational studies, controlled studies, and abstracts from scientific presentations. We reviewed articles meeting the eligibility criteria and abstracted outcome data. Outcomes included study design, number of study subjects and study demographics, description of exposure, personal protective equipment used, duration of symptoms, illness developed, medical evaluation performed, treatment provided, hospitalizations, deaths, drug testing performed, and any situation review performed to prevent illness, analytical confirmation of the identity of culprit agent, and concentrations of drug in serum/blood.

Results: Our search yielded 454 citations after deduplication. After abstract and text review, 12 unique reports met the inclusion criteria. All identified studies were observational studies. Ten of the 12 were Health Hazard Evaluation reports from the National Institute for Occupational Safety and Health; two reports describe the same exposure case. There were no reported instances of comprehensive drug testing using liquid chromatography-mass spectrometry or gas chromatography-mass spectrometry in exposed first responders. Among first responders possibly exposed to fentanyl or fentanyl analogs, none were admitted to the hospital, and only three first responders received naloxone. The three officers who received naloxone lacked recommended personal protective equipment and had subjective improvement of symptoms following naloxone. There were no instances of severe respiratory depression requiring assisted ventilation or hospital admission. Among forensic laboratory technicians, only one instance of detectable concentrations of fentanyl in urine was reported, and there were no instances of symptomatic cases.

Conclusions: Among published reports of 27 first responders with symptoms after possible ambient fentanyl exposure, symptoms, recorded physical findings, and vital signs were inconsistent with acute opioid toxicity. Breaches in the recommended use of personal protective equipment appeared common. Only three persons received naloxone, although none had plausible effects of fentanyl. No suspected exposure to fentanyl led to hospitalization or death. Based on these low-quality data, there were no plausible opioid effects from ambient exposure to suspected fentanyl.

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Introduction

The United States (US) is in the midst of a historic opioid epidemic, with almost 80,411 deaths related to opioids in 2021 alone [1]. Illicitly manufactured fentanyl is implicated in 70% of deaths [2], and while overdoses related to prescription opioids alone are in decline, those involving synthetic opioids other than methadone (most commonly fentanyl and fentanyl analogs) continue to increase [1]. With the increase in fentanyl and fentanyl analogs comes increased casual contact with fentanyl by the lay public, including first responders.

First responders may be exposed to fentanyl and fentanyl analogues along a spectrum of severity. The first and most serious would be *via* aerosolized exposure (i.e., a weaponized formulation designed to maximize inhalation exposures) which has the greatest potential for intoxication. More likely routes of exposure include cutaneous – *via* touching drug paraphernalia or drug powders without barrier protection, such as gloves or long sleeves – inhalation – from droplets of drug liquid or plumes of powder from opening drug bags or baggies – and mucosal exposure – from splash exposure or a responder touching a drug residue and then touching

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their mouth or rubbing their eyes. These latter classes of exposure are expected to be less likely to result in clinical intoxication.

For several years, the lay media has reported numerous cases in which illness was reported as a result of occupational exposure. This concern – described as a "panic" by some [3] – may be in part related to the Moscow Theatre Siege in 2001, in which a weaponized aerosol thought to contain carfentanil and remifentanil resulted in mass public intoxication *via* inhalation [4]. In contrast to the Moscow Theatre Crisis, first responders come into contact with powder as opposed to aerosolized fentanyl. Several statements have contributed to this concern, including several produced by the US Drug Enforcement Agency, stating that "a grain of sand" of fentanyl-containing product could prove fatal [5].

While fentanyl has greater affinity at the mu-opioid receptor – resulting in 50–100x higher potency than morphine – there is a long history of its safe use in the emergency and preoperative setting since 1959, and it is classified as an essential medication by the World Health Organisation [6–9]. In recent years, fentanyl and its structural analogs (some of which are more potent) have been produced by clandestine chemists and have entered into the illicit opioid supply. In overdose, fentanyl produces the classic opioid intoxication findings of CNS depression, miosis, and respiratory depression. Despite the increased potency of fentanyl and its analogues, naloxone – a competitive mu antagonist – remains effective at reversing their clinical effects [10,11].

Amidst the concern and lay media reports of first responder intoxications related to fentanyl and fentanyl analogs, the American College of Medical Toxicology (ACMT) and American Academy of Clinical Toxicology (AACT) published a joint position statement in 2017 stating that basic personal protective equipment (PPE) was sufficient to protect from occupational opioid toxicity [11]. These recommendations consist of an N-95 or P100-rated respirator, nitrile gloves, eye protection, and water-resistant coveralls for dermal and respiratory exposure. [12]. However, at the time of the writing of the ACMT/AACT joint statement, there were little human data to support their findings. We aim to perform a systematic review of the literature to describe illnesses from occupational fentanyl exposure.

Methods

Protocols and registration

We conducted a systematic review following the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (https://www.equator-network.org/reporting-guidelines/prisma/). We registered the review with the Prospero Database (Prospero ID CRD42020194176).

Eligibility criteria

We included studies involving human occupational exposures involving fentanyl and fentanyl analogues described in case reports, case series, observational studies, controlled studies, and abstracts from scientific presentations. We also included NIOSH Health Hazard Evaluation reports, which are not peer-reviewed but field reports of occupational exposure. We only included cases involving human exposures. Consensus statements were excluded. We excluded cases if we were unable to obtain a translation, lay media reports, and animal exposures.

Information sources

Information sources included five electronic literature databases and the National Institute for Occupational Safety and Health (NIOSH). Searches were performed across PubMed on 18 May 2020, EMBASE on 28 May 2020, SCOPUS on 28 May 2020, Web of Science on 29 May 2020, CINAHL on 29 May 2020), and NIOSH on 18 August 2020. Due to the COVID-19 pandemic, there was a delay in fully reviewing these articles. These searches were repeated on 30 June 2022 for NIOSH, PubMed, EMBASE, Web of Science, and CINAHL to account for the advancement of the literature in the meantime. Our institutions' membership to SCOPUS had lapsed in the meantime.

Data collection process

Databases were searched using a combination of controlled vocabulary terms and keywords with Boolean operators, for example, (fentanyl) and (first responders) and (exposure). We tailored search terms and strategies to the syntax and controlled vocabularies of each database, such as using MeSH terms with PubMed. Please see Supplementary Appendix 1 for the full search strategy and list of search terms.

We exported citations from the literature databases into the citation management program EndNote for organization and deduplication. Removal of duplicate studies occurred prior to title/abstract screening. The search strategy is described in Figure 1 using the PRISMA flow diagram format (http://www.prisma-statement.org/).

Two independent reviewers, blinded to author identity and journal, screened studies based on the inclusion/exclusion criteria by reviewing titles and abstracts. This resulted in the removal of 415 studies. Subsequently, they reviewed the included cases in greater depth. Articles were discussed between reviewers for inclusion until a consensus was reached.

The data we collected include study design, number of study subjects and study demographics, description of exposure, PPE used, duration of symptoms, illness developed, medical work-up performed, treatment provided, hospitalizations, deaths, drug testing performed, and any situation review performed to prevent illness, analytical confirmation of the identity of culprit agent, and any concentrations of drug in serum/blood.

Results

Study selection

The original search yielded 652 articles; 198 were removed as duplicates. Four-hundred fifteen studies were excluded

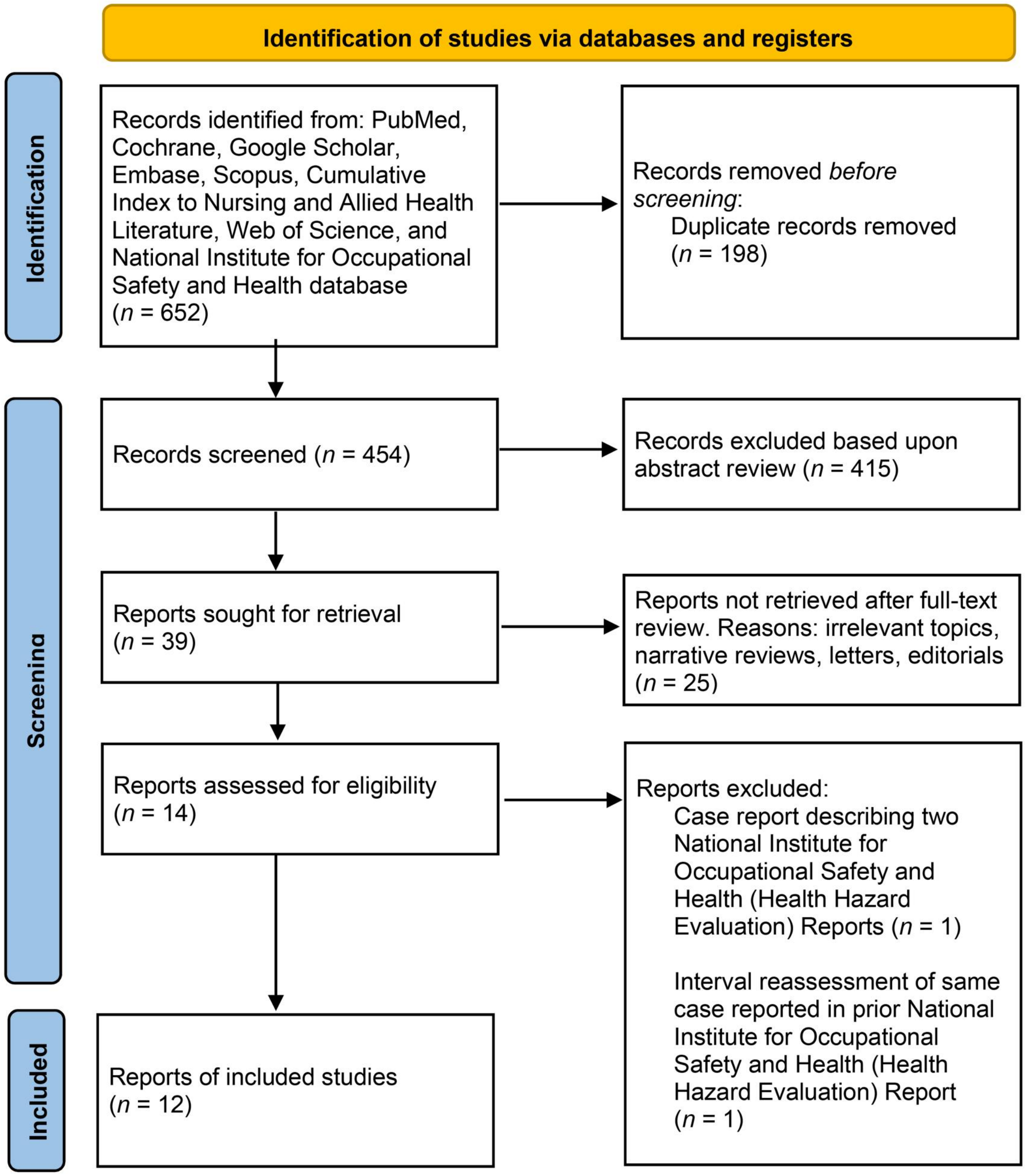

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of search strategy.

after abstract review as they did not include cases of first responder exposure. This search strategy yielded 39 citations. After screening the full text by two reviewers, a further 25 studies were excluded, resulting in 14 studies.

Study characteristics

No controlled trials met the study criteria. All studies we identified were observational studies. The largest study consisted of a self-reported questionnaire of 189 firefighters. The next two largest studies consisted of bio-monitoring and exposure assessment of technicians in forensic laboratories handling evidence. The majority of studies were NIOSH Health Hazard Evaluations ($n = 10$) of either individual exposure incidents or a series of incidents over a period of time; however, two Health Hazard Evaluations describe the same case as an interim and final report [13,14]. Finally, there was one additional questionnaire-based study of law enforcement and one case study involving an emergency medicine pharmacist.

Summary of evidence

We provide the summary of the included cases in Table 1, and narrative summaries of each study are provided in Supplementary Appendix 2. We report a total of 438 individuals assessed for possible occupational exposure to suspected fentanyl and fentanyl analogues. This includes the survey results from 212 first responders regarding fentanyl exposure risks, as well as case evaluations of 25 law enforcement personnel or first responders, 134 were medical examiners involved with fentanyl death autopsies, 66 laboratory

Table 1. Summary of Health Hazard Evaluation reports from the National Institute for Occupational Safety and Health.

Source	Occupation	Exposure description	Personal protective equipment use	Number with any symptoms /number with respiratory depression	Subjective symptoms	Naloxone (Yes/no)	Clinical course	Analytical confirmation
Chiu et al. 2020 [15]	Medical Examiners	Statewide network of medical examiners handled 20 fentanyl overdose deaths (134 examiners evaluated).	Gloves used	0 / 0	No symptoms reported.	No	NA	None
Chiu et al. 2018 [16]	Police Officers	Evaluation of eight individual exposures in 2017. Only seven met criteria for further Health Hazard Evaluation; six of seven cases involved.	Two of eight did not wear gloves.	8 / 0	Chest tightness, difficulty breathing, palpitations, pinpoint pupils, diaphoresis, weakness, and tingling.	No	Six of seven officers were evaluated in the emergency department	Fentanyl analogues identified in three drug samples: cyclopropylfentanyl (2), butyrylfentanyl (1), carfentanil (1), U-47700 (1).
Chiu et al. 2019 [17]	Firefighters	189 fire fighters surveyed on PPE use in situations with suspected opioid exposure.	96% always used gloves. 7% used respirators. 5% used eye protection. 1% used long sleeves.	2 / 0	Headache, numbness, and tingling	No	Mild symptoms in two cases. Unclear if medically observed.	None
Chiu et al. 2018 [18]	Police officer	Exposure to white powder during a vehicle search at a traffic stop	Short sleeves. No gloves.	1 / 0	Disorientation, lightheaded, blurry vision, hypertension	No	Observed in the emergency department with spontaneous improvement.	Fentanyl and metamfetamine detected in powder
Chiu et al. 2018 [19]	Police officers	Response to overdose in hotel room	Short sleeves, gloves, and respirators	4 / 0	Dizziness, sensation of feeling drunk, lightheaded, blurry vision, headache, sensation of warmth, weakness	Yes	Officers observed in emergency department. Symptoms resolved. Discharged.	None
Chiu et al. 2018 [20]	Police officers	Vehicle search at traffic stop. Plume of white powder.	Long sleeve shirts and gloves. No respirators	2 / 1	Dizziness, confusion, difficulty breathing	Yes	A law enforcement officer improved after naloxone. Both law enforcement officer observed in emergency departments. Discharged.	Alprazolam and delta-9-tetrahydrocannabinol identified in drug sample; no opioids confirmed
Chiu et al. 2018 [21]	Deputy Sheriffs and fire/ emergency medical services	Response to a pill party. White syringe with powdery substance.	Long sleeves. Did not wear gloves during entire encounter. No respirators.	8 / 0	Weakness, confusion, palpitations, lightheaded, nausea	No	Eight of nine responders observed on scene. Spontaneous resolution of symptoms.	None

(*continued*)

Table 1. Continued.

Source	Occupation	Exposure description	Personal protective equipment use	Number with any symptoms /number with respiratory depression	Subjective symptoms	Naloxone (Yes/no)	Clinical course	Analytical confirmation
Chiu et al. 2018 [13]; Chiu et al.[14]	Fire/ emergency medical services and police officer	Response to overdose in hotel room. Cardiac resuscitation with ungloved hands	Responder handled the CPR machine without gloves after contact.	1 / 1* *Single recorded respiratory rate of 8 breaths/min without miosis or impaired consciousnes	Warmth, lightheaded, palpitations, increased perspiration, numbness, oral tingling	Yes	Emergency medical service provider received three doses of naloxone with improvement. Observed in emergency department and discharged	Urine drug screen negative for cannabinoids, phencyclidine, cocaine, opiates, amfetamines, benzodiazepines, barbiturates.
Broadwater et al. 2020 [22]	Forensic scientists	Survey of 24 forensic laboratory personnel.	Glove use inconsistent.	1 / 0	No symptoms reported	No	Lightheadedness after exposure to phencyclidine. No effects due to fentanyl	High-performance liquid chromatography for environmental samples, liquid Chromatography with tandem mass spectrometry of urine
Broadwater et al. 2020 [23]	Forensic scientists	Survey of 42 forensic personnel.	Glove use inconsistent.	0 / 0	No symptoms reported	No	Not available	

PPE: Personal protective equipment. CPR: Cardiopulmonary resuscitation.

technicians involved in the processing of drug seizure evidence, and one emergency department pharmacist. Subjective symptoms were reported in 27 individuals. Twenty were monitored in the emergency department, and only three received naloxone. There were no hospitalizations or deaths. There were no reports of miosis, loss of consciousness, stupor, coma, or other findings of a depressed central nervous system depression consistent with opioid intoxication in any case. The most common subjective symptoms were nonspecific to opioid intoxication and included warmth, light-headedness, diaphoresis, and palpitations.

Naloxone administration was reported in three instances. In the first, one officer received naloxone without any symptoms of miosis or respiratory depression [19]. In the second, a decreased respiratory rate of 8 breaths/min without associated miosis or impaired consciousness was observed [13,14]. In the third case, an officer described "difficulty breathing" and was given naloxone. He was not observed to have objective respiratory depression [20]. In these three cases, a breach in PPE, as recommended by the ACMT/AACT was reported.

Analytical confirmation was available in six studies. One law enforcement officer was exposed to powder which was confirmed as fentanyl [18]. One study identified fentanyl analogs in drug samples that law enforcement officers were exposed to – consisting of cyclopropylfentanyl ($n = 2$), butyrylfentanyl ($n = 1$), carfentanyl ($n = 1$) [16]. Despite cyclopropylfentanyl, butyrylfentanyl, and carfentanyl being identified in drug residues symptomatic officers were exposed to, no officers received naloxone in these instances. One study involved the case of a pharmacist who experienced dermal exposure after spilling an aqueous solution containing 380 µg of fentanyl on an ungloved hand with a healing laceration – no clinical signs/symptoms were observed [24]. One officer receiving naloxone underwent a seven-drug urine drug screen, which did not detect the presence of cannabinoids, phencyclidine, cocaine, opiates, amfetamines, benzodiazepines, or barbiturates, but fentanyl was not part of the screen [13,14].

The remaining two studies, by Broadwater et al. [22,23], were designed to assess exposure to fentanyl amongst forensic technologists who handle fentanyl samples in a criminal analytical laboratory that utilizes liquid chromatography-mass spectrometry for comprehensive drug analysis. These were NIOSH evaluations of exposure among forensic chemists working in controlled substance laboratories processing samples that had been confiscated during law enforcement activities. In the first study [22], fentanyl was detectable on post-shift hand swabs in 9/13 samples (range 2.7–11 ng/swab), while fentanyl was detectable in the personal air space of 4/12 (range 0.004–0.31 $\mu g/m^3$) samples and on the workplaces swabs of 18/22 samples (range 0.0012–0.37 $\mu g/100\ cm^2$). None of the pre-shift hand swabs were positive for fentanyl. In the second Broadwater study [23], hand samples from the beginning and end of the workday were performed. Fentanyl was detectable on 13/18 of hand swabs at the end of the working day – and only one individual had fentanyl detected on their hand swab at the beginning of the day (although their end-of-day hand swab exceeded the concentration observed at the beginning of the day). The range of detected fentanyl was 1.1–750 ng/wipe, while fentanyl was detectable in the personal air space of 2/18 (range 0.0051–0.01 $\mu g/m^3$) samples and on the workplace swabs of 38/46 samples (range 0.0015–0.42 $\mu g/100\ cm^3$). Of urine samples, 1/18 forensic technologists had fentanyl and norfentanyl in their urine at concentrations of 0.045 µg/L and 0.088 µg/L, respectively [23]. There were no instances of adverse effects reported. National Institute for Occupational Safety and Health evaluators observed numerous breaches of laboratory PPE and protocol that could have increased exposure risk.

Attaway et al. [5] surveyed five law enforcement agencies serving jurisdictions with high rates of opioid use about first responder knowledge of fentanyl risks. While "nearly all" were worried about fentanyl exposure, most had not received training on safe handling. One agency had officers wear gas masks and gloves while field testing any powder or pill. "Most" officers stated they wore gloves when responding to possible fentanyl-related calls. One officer stated that he learned that fentanyl can be "absorbed through your skin pores, or you can inhale it and overdose yourself" through exposure to a US Drug Enforcement Agency video during one of their in-training examinations. Although over "one-third" of officers had "heard of" someone in their agency overdosing, no officer could confirm exposure. Two officers stated they were exposed but were asymptomatic. A subset of law enforcement leadership was surveyed to see if they were aware of the AACT/ACMT Joint Statement. They were unaware of these recommendations [5]

Discussion

Overall, there were few reports of occupational illness reported in the literature. Of those reports, we identified zero cases of opioid toxidrome, death, and hospitalization. Drug testing for fentanyl was primarily limited to industrial settings with worker monitoring. In studies of forensic chemists, we noted evidence of possible occupational exposure as evidenced by the presence of fentanyl in the personal air samples, bench top swabs, and hand swabs, but in the only study that analyzed urine, detection of fentanyl occurred in only one individual out of 18 tested, and no evidence of toxicity was observed [22,23].

With 10,000 pounds of fentanyl powder and 50.6 million fentanyl-containing pills seized in 2022 by law enforcement, first responders across many jurisdictions are in the presence of fentanyl on a daily basis [1,25]. Despite these trends, published cases of occupational intoxications appear nonexistent. We would predict more fentanyl-related illnesses being reported if occupational fentanyl exposure was a significant risk.

While occupational exposure appears less dangerous than what is described in the lay media, breaches in basic personal protective equipment are a recurrent theme in symptomatic cases. Additionally, studies would be helpful to clarify what PPE is needed. Surveys of law enforcement and first responder questionnaires suggest confusion continues to exist about correct PPE practices [26]. The three cases we reported in which naloxone was administered involved breaches in recommended PPE usage [13,14,19,20].

Unintentional intoxication from fentanyl and fentanyl analogs also seem unlikely from a pharmacokinetics standpoint. Fentanyl is a small hydrophilic molecule which lends itself well to dermal formulations, and fentanyl is commonly used in patch form for chronic pain [27]. While fentanyl transdermal patches are implicated in numerous deaths, they function by creating a subcutaneous depot that slowly distributes in the body, reaching a steady state in 24–26 h and requiring a similar amount of time for the depot of fentanyl to redistribute once the patch has been removed [26,28]. This would be less likely to cause acute symptoms on contact [28]. In practice, first responders are not going to wait that long to wash off cutaneous fentanyl. While fentanyl has nearly 100% bioavailability *via* the inhalational route [28], it has very low vapor pressure and is unlikely to form a vapor in the environmental conditions in which people commonly work. For instance, if an unprotected worker was exposed to the highest observed airborne concentrations of fentanyl found during manufacturing, it would take 200 min to reach a dose of 100 µg based upon the time-weighted average occupational exposure limits (OEL-TWA) [29,30]. Pragmatically, these scenarios are far beyond what first responders experience.

We want to ensure the safety of our police and first responders, yet there was an increase in deaths among law enforcement officers in 2020 and 2021, according to the National Law Enforcement Officer Memorial [31]. Amidst the opioid epidemic, the Federal Bureau of Investigation reported that there were no overdose deaths among officers who died in the line of duty [32]. Working to increase the outreach of the 2017 expert opinion may serve to help dispel misconceptions about fentanyl risk. It has been demonstrated that brief training modules regarding the low risk of acute overdose from touching or inhaling fentanyl are effective at correcting misperceptions among law enforcement agents [33].

Limitations

Our study is subject to the typical study design limitations of systematic reviews, including publication bias. We were not able to view the medical records or evaluate any of the patients. Lack of drug testing for fentanyl prevents us from definitively saying if first responders were exposed to fentanyl or to another agent or suffering from other psychologic effects. Knowing if fentanyl was or was not present definitively would give a more accurate clinical picture. Similarly, only bio-monitoring studies were performed on laboratory technicians, and we do not know how many law enforcement officers, firefighters, or emergency medical technicians were exposed to fentanyl at subtoxic doses.

The quality of data is poor. The majority of reports are from NIOSH Health Hazard Evaluation reports. The NIOSH reports are prepared for the US Government by trained physicians but do not undergo a peer review process and rely on recall of the patient. Additionally, the NIOSH reports are not routine following each incident and need to be invited. Due to the process of activating NIOSH, there may be selection bias, and there may be cases that were missed because NIOSH was not activated. The NIOSH reports attempt to reflect the history and physical examination and generally stop short of making conclusions. For example, subjective improvement with naloxone is not evidence of opioid toxicity if signs and symptoms of opioid toxicity are not present before naloxone. The questionnaire-based study of Attaway et al. [5] is limited by the recall bias of the interviewed officers and selection bias of the included agencies; moreover, participants may not have been aware of the purpose of the study. Finally, there may have been exposure cases that were simply clinically managed in emergency departments and not reported or written as case reports, and consequently not reflected in the literature. Overall, the quality of peer-reviewed literature is of poor quality.

Conclusions

Among published reports of 27 first responders with concern for symptoms after possible ambient fentanyl exposure, symptoms, recorded physical findings, and vital signs were generally inconsistent with fentanyl effects. Breaches in the recommended use of PPE appeared common. Only three persons received naloxone, although none of these displayed definitive signs of the opioid toxidrome. No suspected exposure to fentanyl led to hospitalization or death. Based on these low-quality data, there were no plausible opioid effects from ambient exposure to suspected fentanyl.

Disclosure statement

No potential conflict of interest was reported by the authors.

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