

# Fentanyl and the safety of first responders: Science and recommendations

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Opioids have many beneficial uses in medicine, but, taken inappropriately, they can cause life-threatening health effects. The increasing use of physician-prescribed and illicit opioids, including highly potent fentanyl and its analogs, have contributed to a significant increase in opioid-related drug overdoses in the United States, leading to a public health emergency. There have been a number of reports describing adverse health effects experienced by police officers, fire-fighter emergency medical services providers, and private sector ambulance personnel when responding to drug overdose incidents. Several sets of exposure prevention recommendations for first responders are available from government and the private sector. Understanding the scientific basis for these recommendations, increasing awareness by responders of the potential risks associated with opioid exposure during a response, and educating responders about safe work practices when exposure to opioids is suspected or confirmed are all critical prevention measures that can keep first responders safe.

## KEYWORDS

fentanyl, first responders, opioid crisis, safe work practices

## 1 | INTRODUCTION

The role of opioids in anesthesia, pain relief, and in other acute and chronic disorders is well-established, but opioid overdoses can have life-threatening effects by causing respiratory depression and apnea.<sup>1</sup> The widespread use and misuse of physician-prescribed opioids, the diversion of legally prescribed opioids for illicit use, and the manufacture and distribution of illicit opioids such as heroin, have resulted in an increasing number of drug overdose deaths in the United States. In October of 2017, President Trump characterized the opioid epidemic as “the worst drug crisis in American history” declared it to be a public health emergency,<sup>2,3</sup> chartered a presidential commission to make recommendations to address the epidemic,<sup>4</sup> and proposed \$10

billion in funding to combat the epidemic.<sup>5</sup> There is ample evidence of the severity of the epidemic.<sup>6</sup>

In 2017, the Centers for Disease Control and Prevention (CDC) reported that drug overdose deaths in the United States more than tripled from 1999 to 2015.<sup>7</sup> The epidemic continues to grow. From 2015 to 2016, opioid overdose deaths increased by more than 20%—rising from 52 898 in the year ending in January 2016 to 64 070 deaths in the year ending in January 2017.<sup>8</sup> The epidemic appears to be affecting life expectancy in the United States. In 2016, US life expectancy declined for the second year in a row caused in part by an increase in unintentional injuries, chiefly drug overdoses.<sup>9,10</sup>

Although the recent increase in overdose deaths coincides with an increase in opioid prescribing practices beginning in the mid-1990s, there has also been a parallel increase in drug overdose deaths from diverted or illicitly manufactured, synthetic opioids such as fentanyl and its various analogs (“fentanyls”).<sup>7</sup> Recent implementation of voluntary opioid physician prescribing guidelines<sup>11</sup> and physician prescribing restrictions<sup>12</sup> is reducing the use of licit opioids,<sup>13</sup> but not the use of illicit opioids, specifically heroin and fentanyls.<sup>14</sup>

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In December of 1959, fentanyl was first synthesized for use as an intravenous general anesthetic and has become one of the world's most frequently used opioid analgesics.<sup>15</sup> By the 1990s, rapid onset, transdermal patches containing fentanyls were introduced for chronic pain relief in opioid-tolerant individuals.<sup>16</sup> Fentanyl is also supplied in other quick-acting formulations for transmucosal delivery by means of an oral lozenge or flavored lollipop, a buccal tablet, and as a sublingual tablet or spray.<sup>15,17</sup>

Fentanyl itself is 50-100 times as potent as morphine based on the drug's affinity for the mu-opioid receptors of the respiratory control center located in the brainstem.<sup>18,19</sup> A small amount of fentanyl can relieve severe pain,<sup>20</sup> but it also can cause acute intoxication leading to respiratory depression if not taken appropriately. Due to the narrow range between the value of its effective or therapeutic dose (ED<sub>50</sub>) and its lethal dose (LD<sub>50</sub>),<sup>21</sup> there is a risk of "making a mistake" which often leads to a lethal overdose.

Fentanyl analogs, such as acetylfentanyl,<sup>22</sup> butyrfentanyl,<sup>23</sup> and furanylfentanyl,<sup>24</sup> are equally potent and have caused multiple overdose deaths. Carfentanil, a fentanyl analog, is used as a tranquilizing agent to rapidly sedate wildlife and as a large animal general anesthetic in veterinary medicine. It is 10 000 times as potent as morphine.<sup>25,26</sup> Unintentional use of illicitly manufactured fentanyls alone, added to heroin, cocaine, or to counterfeit prescription tablets resembling oxycodone or hydrocodone, has been cited as an important driver of the recent increases in opioid overdose deaths.<sup>27,28</sup>

There have been many reports detailing symptoms that first responders have developed when responding to drug overdose incidents in environments where multiple types of illicit drugs may be present.<sup>29-32</sup> These reports have involved public sector police officers and fire-fighter emergency medical service providers, as well as emergency medical service providers that are part of the public safety model but separate from police and fire departments. While the types of events where first responders experience acute symptoms deserve careful study, it is very difficult to examine rapid response situations retrospectively. Although the exact physiologic relationship between the multiple drugs that may be present during any particular response incident, and the adverse health effects some responders have experienced during a response incident is uncertain, there is no doubt that these ill effects occur in relationship to work activities. Training aimed at improving workers' understanding about what routes of exposure and specific job tasks can put a first responder at risk of the adverse health effects arising from multiple drug exposure, and the actions responders can take to protect themselves, is critically important.

Determining what steps should be taken on a precautionary basis to protect first responders from the potential adverse effects of exposure to opioids such as the fentanyls encountered during job tasks has become the subject of several sets of recommendations from government and the private sector for protecting first responders. This commentary provides an overview of the scientific information used in developing the existing prevention recommendations, including information about opioid pharmacology, routes of exposure, signs and symptoms of opioid intoxication and their medical management to assist first responders, police and fire department management,

clinicians, and other interested parties in understanding the current scientific basis for prevention recommendations. It is important that any prevention recommendation developed for the current opioid crisis be based on published, peer-reviewed, scientific findings.

## 2 | PHARMACOLOGY

Opioids exert their pharmacologic actions through four different opioid receptor systems: mu ( $\mu$ ); delta ( $\delta$ ); kappa ( $\kappa$ ); and opioid receptor like-1 (ORL1).<sup>33</sup> These opioid receptors are distributed both centrally in the brain and brain-stem, and peripherally in the spinal cord, peripheral nerves, and in the small intestine. In the brain-stem, mu opioid receptors modulate the respiratory center's responses to low levels of oxygen (hypoxemia) and high levels of carbon dioxide (hypercarbia).<sup>34</sup> Binding at the mu receptor is responsible for the respiratory depression seen in opioid overdoses by reducing the sensitivity of the chemoreceptors in the brainstem to hypercarbia and by depressing the ventilator response to hypoxemia.<sup>34</sup>

Although mu opioids are very effective analgesic medications, they also enhance mood by activating central dopamine reward pathways, producing intense feeling euphoria.<sup>33</sup> The reward effect is especially strong when the drug is delivered rapidly into the brain,<sup>35</sup> by injection or when insufflated through the nose ("snorting").<sup>36</sup> Individuals who are treated with long-term opioid therapy develop tolerance to increasing doses and dependence to varying degrees with about 25% becoming nonmedical users, and 10% developing features of addiction.<sup>37</sup> Changes in the cellular physiology pathway involving cyclic adenosine monophosphate (cAMP) play a role in the development of opioid tolerance and dependence.<sup>38</sup> After opioid binding to the mu receptor, the mu receptor experiences a progressive inability to propagate a signal and the receptor becomes desensitized.<sup>39</sup> As a result, the dose of opioids has to be increased to achieve the desired analgesic effect.<sup>40</sup>

An individual who is unaccustomed to taking opioids is said to be an opioid-naïve individual. Opioid-tolerant individuals are those who take at least 60 mg of oral morphine per day (or an equianalgesic dose of another opioid).<sup>41</sup> Whether a person is opioid-tolerant or opioid-naïve has important consequences in their physiologic reaction to opioids.

The current goals of opioid pharmacology are to develop opioid formulations with abuse-deterrent properties to make them harder to manipulate for injecting or snorting,<sup>42,43</sup> and to identify opioid agonists that would activate anti-nociceptive signaling without causing mu-agonist euphorogenic responses.<sup>44</sup> Recent studies of the structure of the mu receptor have demonstrated an analgesia signaling pathway and a separate rewarding and respiratory-depressing pathway that could lead to analgesic-specific opioids without the euphoric effects.<sup>45</sup>

## 3 | EXPOSURE PREVENTION

Acute opioid intoxication can potentially occur in occupational settings. Workers with anticipated occupational exposure to opioids

in any form, including powders, liquids, pills, sprays, films gels, or adhesives should be aware of potential routes of exposure they may encounter in performing their jobs.

### 3.1 | Inhalation

A potentially important occupational route of exposure to opioids may occur by breathing air contaminated with airborne opioid particles in the respirable range, that is, less than 10  $\mu\text{m}$  in diameter.<sup>46</sup> During emergency response situations, powder-like fentanyls may become airborne by disturbing surfaces, brushing powder from clothing, or other incidental activities that cause powder aerosolization.

Pharmacokinetic studies demonstrate fentanyl delivered to the airways by an aerosolized mist, or as a free or liposome-encapsulated particle, achieves measurable plasma concentrations within minutes to hours.<sup>47,48</sup> Although these studies demonstrate that fentanyl can be effectively administered by the inhalational route and achieve an effective analgesic dose, it is uncertain what level of airborne exposure would result in acute intoxication resulting in lethal respiratory depression in an occupational setting. The only published report of human inhalational exposure concerns the unconfirmed use of carfentanil and remifentanil (and halothane) during the 2002 Moscow theater siege which resulted in 125 fatalities.<sup>26,49</sup> However, the Moscow theater situation differs from a typical emergency response situation in that the inhalational exposure during the theater siege may have been to a very large quantity of uniformly respirable particles, that is, "weaponized" for maximum inhalational effect.

First responders entering an environment where airborne particles are not suspected or confirmed, but small amounts of powder are visible, should wear an N-100, P-100, or R-100 respirator.<sup>50</sup> Examples of this type of emergency response activity include responding to an overdose call or traffic stops where drugs are suspected. Since no occupational exposure limit has been established for fentanyl, using the filter with the highest efficiency, and reducing face seal leakage as much as possible through proper fit testing and training, provides effective respiratory protection.<sup>50</sup> First responders entering an environment where airborne fentanyls are strongly suspected or confirmed to be present should wear a supplied air respirator (SAR) or self-contained breathing apparatus (SCBA) to provide maximal protection.<sup>50</sup> Examples include hazardous material incident responses and law enforcement tactical operations where large volumes of powder are observed and/or where uncontrolled aerosolization is likely.

### 3.2 | Mucous membranes

As important as inhalation is as a potential route of exposure, the inadvertent contact of fentanyls with the mucous membranes of the eye, nose or mouth presents an equivalent hazard. Fentanyl is 65% bioavailable when delivered by buccal or sublingual administration—a 40  $\mu\text{g}$  buccal tablet leads to similar plasma concentrations (1 ng/mL) as a 10 mg transdermal patch in substantially less time (45 min vs 72 h).<sup>51</sup>

In the sole published report of symptomatic acute intoxication resulting from occupational exposure to carfentanil, a 42-year old,

previously healthy veterinarian was splashed in the eyes and mouth while pulling from a tree a tranquilizing dart that was intended for an elk which contained 1.5 mg of carfentanil and 50 mg of xylazine hydrochloride, an  $\alpha_2$  adrenergic receptor agonist.<sup>52</sup> The veterinarian immediately washed his face with water, but became drowsy within 2 min. He was administered 100 mg of naltrexone (a partial opioid antagonist) intramuscularly and his vital signs returned to baseline in 1 h.<sup>52</sup>

Given the potential risk of mucous membrane exposure, eye goggles, face shields, and mouth protection are part of a prudent prevention measure for exposed workers.<sup>50</sup> Importantly, touching the eyes, nose, or mouth after touching a contaminated individual, surface, or object should be avoided.<sup>50</sup> Gloves should be changed regularly during an incident response as it would be difficult to spot a small amount of drug on a contaminated glove, skin, clothing, surface, or object.<sup>50</sup>

### 3.3 | Dermal

Fentanyls have been known to be able to penetrate human skin due to their lipophilicity<sup>45,53,54</sup> and low molecular weight.<sup>55</sup> Dermal exposure to fentanyls may be of more importance in chronic, low-level, occupational exposure than in the acute, low-level exposures that are typical of emergency response incidents.<sup>56</sup>

Data on transdermal fentanyl toxicity may be inferred from clinical studies on a transdermal patch system designed for sustained fentanyl delivery. How fast fentanyl achieves a measurable plasma concentration, and how fast the drug can gain access to the central nervous system to cause symptoms of acute intoxication and respiratory depression, determines the risk to workers. Fentanyl has a very long lag time—approximately 10 h.<sup>57</sup> It takes 2 h after patch placement to achieve a measureable plasma concentration<sup>58</sup> and from 8 to 37 h to achieve full clinical effects.<sup>20,59–61</sup> Symptoms of acute opioid intoxication resulting from incidental dermal contact with fentanyl appears to be an unlikely occurrence.<sup>62</sup> Even so, some police departments are abandoning their historical practice of doing field tests for narcotics out of a concern about inhalational or dermal exposure to fentanyls.<sup>63,64</sup>

A prudent prevention measure to prevent transdermal exposure is to wear non-powder, nitrile gloves, 5  $\pm$  2 mm (mil) thickness, to protect against transdermal exposure.<sup>50</sup> If the skin becomes contaminated during a response incident, the skin should be washed promptly with soap and copious amounts of water.<sup>50</sup> Soap solubilizes fentanyl, which is poorly soluble in plain water, and soap aids in decreasing surface attraction, making fentanyls more easily removable from the surface of contaminated skin. Use of hand sanitizers and hand wipes should be avoided as their use may spread the fentanyls to previously uninvolved skin areas.<sup>50</sup>

### 3.4 | Ingestion

Potential exposure to opioids may occur by ingestion if food or beverages become contaminated with opioids. Where fentanyls are suspected or confirmed to be present, it is prudent for responders not

to eat, drink, or smoke. In addition, touching the mouth after touching contaminated objects of equipment can result in ingestion of opioids.<sup>50</sup>

### 3.5 | Percutaneous

Potential exposure to opioids may occur through the percutaneous route if contaminated needles or sharps penetrate intact skin. Multiple incidents of parenteral exposure through handling injectable anesthetics containing highly potent fentanyl and other tranquilizing agents used in veterinary medicine has been reported in the literature and in an online survey.<sup>65</sup>

## 4 | ACUTE OPIOID INTOXICATION

The most specific and life-threatening sign of an acute opioid intoxication is depression of respiratory activity.<sup>66</sup> Miosis and stupor may also be present, but all these signs are not consistently present and individually can be due to effects of other drugs.<sup>40</sup> A respiratory rate of 12 or fewer breaths per minute in a person who is not at physiologic sleep has been shown to have an 80% sensitivity for predicting who would respond to administration of the opioid reversal agent naloxone.<sup>40,67</sup> Hypoventilation, or shallow breathing, may be an early sign of acute intoxication as opioids reduce tidal volume before the respiratory rate.<sup>68</sup>

Respiratory depression leading to shallow breathing or apnea is the most life-threatening toxic effect of acute opioid intoxication. Acute intoxication can also cause the gradual onset of central nervous system symptoms such as lightheadedness, drowsiness, nausea and vomiting, and dizziness.<sup>69</sup> These signs and symptoms, occurring in a worker in an occupational setting where exposure to fentanyl is suspected or confirmed, should not be discounted and should be managed as an acute opioid intoxication.

## 5 | MANAGEMENT OF ACUTE OPIOID INTOXICATION

Signs of respiratory depression in situations where a worker's occupational exposure to fentanyl is suspected or confirmed requires immediate medical intervention.<sup>70</sup> The highest priority intervention is the provision of respiratory support by the use of bag-valve mask (BVM) ventilation or, if a BVM is not available, through rescue breaths using standard cardio-pulmonary resuscitation techniques. Following the provision of ventilator support, acute opioid intoxication management in the era of potent respiratory depressants like the fentanyl includes administration of titrated pharmacologic naloxone doses.<sup>71</sup>

Naloxone can rapidly counteract the respiratory depression, sedation, miosis, and analgesia caused by opioids through competitive antagonism at the mu, delta, and kappa opioid receptors.<sup>72</sup> If available, naloxone should be administered when signs of acute drug intoxication are present, although more study is needed to determine optimal out-of-hospital protocols.<sup>73</sup> Naloxone is unlikely to have any ameliorative effect if the signs and symptoms are not due to an opioid intoxication but another type of medical event or different type of drug intoxication. However, its

administration should not be withheld since complications attributed to naloxone administration are exceedingly rare.<sup>74</sup> Even in opioid-tolerant individuals who are taking opioids, low-doses of naloxone can restore breathing without causing opioid withdrawal symptoms.<sup>75</sup>

When used intravenously, naloxone at an initial dose of 0.4 mg has a rapid onset of action, but a short duration of action.<sup>76,77</sup> Naloxone can also be given by intranasal administration, or by using an auto injector against a person's upper leg or shoulder for intramuscular administration. Individuals who ingest fentanyl analogues may require escalating doses of naloxone to produce an effective response.<sup>40,78</sup> An indication of the greater potency of opioids that play a role in overdose responses is the increased frequency of multiple naloxone administrations by first responders.<sup>79</sup> A recent advisory by the US Surgeon General emphasizes "knowing how to use naloxone and keeping it within reach can save a life."<sup>80</sup>

All workers who experience signs or symptoms that may be related to acute opioid intoxication, with or without the need for naloxone administration or BVM ventilation support, should undergo follow-up medical evaluation.

## 6 | RECOMMENDATIONS

Measures that are designed to protect first responders from occupational exposure to fentanyl are available from a number of public and private sector sources. These sources include (1) White House Safety Recommendations for First Responders<sup>81</sup>; (2) National Institute for Occupational Safety and Health (NIOSH)<sup>50</sup>; (3) Drug Enforcement Administration<sup>82</sup>; (4) American College of Medical Toxicology and the American Academy of Clinical Toxicology<sup>62</sup>; (5) the Interagency Board (IAB)<sup>83</sup>; and (6) emergency medical providers.<sup>84</sup> Recommendations in these sources address the following: (1) safe work practices when fentanyl is suspected or confirmed to be present in an occupational setting; (2) training personnel in safe work practice and the appropriate use of medical countermeasures like naloxone; (3) the types of personal protective equipment (PPE) needed to protect workers; and (4) decontamination methods.

The recommendations contained in these sources are consistent across safe work practices, training and PPE. The only differences occur with regard to respiratory protection. When the potential exists for small amount of a powder suspected to be a fentanyl to be aerosolized, NIOSH and the IAB recommend an N/P/R-100 series respirator; ACMT/AECT recommends an N-95 or P-100, and the DEA recommends an N-95. The White House recommends a properly fitted, NIOSH-approved respirator. The IAB currently has the most comprehensive recommendations on decontamination methods. NIOSH and the IAB recommendations are more directly utilizable by first responders as both categorize risk and correlate risk categories to specific job categories. The White House Safety Recommendations for First Responders includes a very helpful section on what a responder should do if the responder or the responder's coworker exhibits any signs or symptoms of acute intoxication.

Any source of recommended prevention measures is for general guidance. Each response situation must be assessed individually to

determine the risks to workers and how best to prevent exposure in specific circumstances. Furthermore, as new information about the risk of opioid exposure in occupational settings emerges, changes in recommended prevention measures for first responders may occur but must be based on sound science. Attention to these changes is critical to providing the most up-to-date worker protection recommendations.

## 7 | CONCLUSION

The current opioid crisis involving potent fentanyl has resulted in a significant loss of life from the use and abuse of licit and illicit opioids. While responding to an emergency incident involving a life-threatening acute opioid intoxication, first responders may be at risk of acute opioid intoxication themselves. Although the precise risk from any particular response incident is not known at the present time, reports of various adverse health effects in first responders during emergency responses to opioid overdoses require that prudent prevention measures be taken to protect their health and safety. As the potential for exposure to potent synthetic opioids increases during emergency response incidents, all recommendations aimed at protecting first responders from risks of opioid intoxication need to be based on published, peer-reviewed, scientific findings.

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The authors made all the contributions to the conception or design of the paper and the acquisition, analysis, and interpretation of data for the paper. The authors drafted the paper and provided final approval of the version to be published. The authors agree to be accountable for all aspects of the paper in ensuring that questions related to the accuracy or integrity of any part of the paper are appropriately investigated and resolved.

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