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# Overdoses due to fentanyl and its analogues (F/FAs) push naloxone to the limit

Joseph V. Pergolizzi Jr MD<sup>1,2,3</sup> | Albert Dahan MD, PhD<sup>4</sup> | Jo Ann LeQuang BA<sup>1</sup> | Robert B. Raffa PhD<sup>2,3,5,6</sup> 

<sup>1</sup>NEMA Research Inc, Naples, FL, USA

<sup>2</sup>Neumentum Inc, Summit, NJ, USA

<sup>3</sup>Enalare Therapeutics Inc, Princeton, NJ, USA

<sup>4</sup>Leiden University Medical Center, Leiden, The Netherlands

<sup>5</sup>College of Pharmacy (Adjunct), University of Arizona, Tucson, AZ, USA

<sup>6</sup>Temple University School of Pharmacy, Philadelphia, PA, USA

## Correspondence

Robert B. Raffa, Tucson, AZ 85718, USA.  
Email: robert.raffa@gmail.com

## Abstract

**What is known and Objective:** Food and Drug Administration (FDA) risk evaluation and mitigation strategies (REMs) encourage emergency responders, paramedics, law enforcement agents, and even laypeople to be trained in the administration of naloxone with the intent of rescuing individuals from a known or suspected opioid overdose.

**Comment:** Although naloxone is generally safe and effective at reversing respiratory depression caused by a conventional opioid such as morphine or heroin by competing with the opioid and displacing it from the  $\mu$ -opioid receptor, questions increasingly are arising as to whether naloxone can adequately reverse opioid overdoses that may involve the potent opioids fentanyl and its analogues (F/FAs). In other words, as more and more opioid overdoses involve F/FAs, can naloxone keep up?

**What is new and Conclusion:** As a competitive antagonist at  $\mu$ -opioid receptors, naloxone is often a life-saving agent in cases of overdose caused by conventional opioids, but it may not be versatile or powerful enough to combat the rising tide of overdoses due to fentanyl and its illicit analogues, or in cases of overdose involving combinations of opioids and non-opioids.

## KEYWORDS

fentanyl, fentanyl analogue, naloxone, opioid overdose

## 1 | WHAT IS KNOWN AND OBJECTIVE

The introduction of the synthetic opioid fentanyl into medical practice in 1960 presented a great advance for surgical anaesthesia,<sup>1</sup> because fentanyl produces efficacious and rapid-onset analgesia. It also shares the adverse effects of opioids, including dose-dependent respiratory depression.<sup>2</sup> Because of its high potency, it presents a particular danger for those who experience an overdose.

Numerous fentanyl analogues (FAs) have been developed (eg alfentanil, carfentanil, remifentanil and sufentanil), which also have important veterinary and/or medical applications. But hundreds of illicit FAs have been synthesized in clandestine laboratories. They are widely available as cheap and powerful drugs of abuse either alone or as adulterants.<sup>3</sup> The legitimate FAs are Schedule II agents

under the Controlled Substances Act (CSA). Many illicit FAs are classified as Schedule I,<sup>2</sup> but newly synthesized FAs fall into a regulatory loophole in that the Drug Enforcement Administration (DEA) cannot schedule a drug about which it is unaware.<sup>4,5</sup>

F/FA are selective and potent agonists at  $\mu$ -opioid receptors (MOR). Because they are highly lipid soluble, they can penetrate the blood-brain barrier readily,<sup>6</sup> allowing overdose to occur more rapidly than with other opioids such as morphine.<sup>7</sup> The high lipophilicity allows it to equilibrate rapidly between serum and cerebrospinal fluid, allowing respiratory depression to occur quickly.<sup>8</sup>

The high affinity of F/FAs for MOR necessitates larger doses of naloxone than required for other opioids.<sup>2</sup> It has also been suggested that fentanyl is a "biased ligand" toward the arrestin pathway, which is more associated with respiratory depression.<sup>7,9</sup>

In some cases, fentanyl is mixed with filler to create a cheap counterfeit of heroin or pressed into pill form and marketed as a diverted prescription opioid.<sup>3</sup> Those who use these drugs may not be aware of the actual contents, or may not understand their potency and potential danger. F/FAs are also frequently combined with other drugs. The net result is that F/FAs have been detected in an increasing number of post-mortem studies of overdose decedents.<sup>10,11</sup>

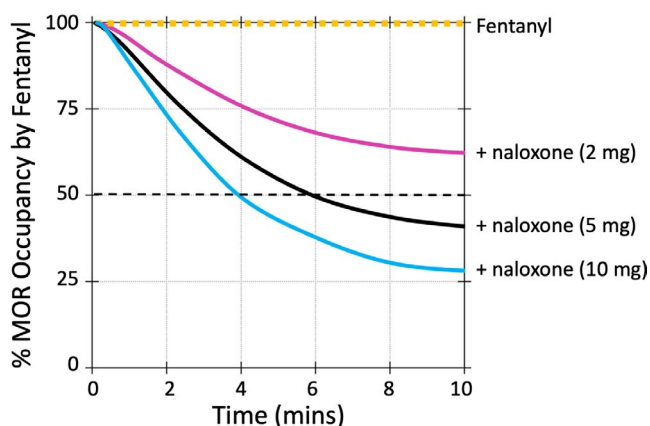
## 2 | COMMENT

### 2.1 | Unique pharmacology of F/FAs

F/FAs have unique pharmacologic characteristics and uniquely potentially dangerous properties in overdose compared to other opioids. This contributes to their resistance to the conventional opioid reversal agent, naloxone.<sup>12</sup> As a result, high doses and multiple administrations of naloxone can be required to reverse F/FA overdose,<sup>13</sup> and even then, it is not always sufficient to rescue a person from an overdose.<sup>14</sup>

In a study that examined three fentanyl dosing levels, a model was developed that would predict how naloxone and fentanyl would interact at MOR. At a dose of fentanyl of 25 or 50 ng/mL, 2 mg IM naloxone decreased fentanyl occupancy of MOR by  $\geq 50\%$ . At 75 ng/mL fentanyl, 2 mg IM naloxone failed to reduce fentanyl occupancy at MOR by 50% (Figure 1).<sup>15</sup> This suggests that in some cases of high-dose F/FA use, naloxone may not be adequate to compete, and that simply increasing the naloxone dose may not improve results.<sup>15</sup>

In an animal model, fentanyl produced apnoea within 14 s, followed by a low tidal volume with slow frequency.<sup>16</sup> When naloxone was administered at fractional inspired oxygen tension at a rate below 10%, the naloxone had no effect. When PaO<sub>2</sub> levels reached 16 mm Hg, no recovery of respiration occurred. Thus, fentanyl-induced apnoea can be resistant to rescue naloxone.<sup>16</sup>



**FIGURE 1** Quantitative model of the displacement of fentanyl binding at the  $\mu$ -opioid receptor (MOR) by intramuscular (IM) administration of naloxone (2, 5, 10 mg). The 2 mg dose of naloxone failed to reduce MOR occupancy by fentanyl by 50%. From Ref [15], with permission

### 2.2 | The Special Challenge of Wooden-Chest Syndrome

F/FAs induce a rapid closure of the vocal cords (laryngospasm) combined with muscular rigidity in the chest wall and diaphragm. Pulmonary complications using therapeutic doses of fentanyl for surgical anaesthesia were reported as early as 1983.<sup>17</sup> This unusual fentanyl-induced respiratory muscle rigidity has been called "wooden chest syndrome" (WCS). WCS may occur at F/FA doses within the therapeutic range, have a rapid onset of about 1–2 minutes after IV injection and may last as long as 15 minutes. Based on animal models, WCS involves an action at the locus coeruleus (LC), which increases noradrenergic outflow. Fentanyl injected directly into the LC induces WCS in about 60 s.<sup>18,19</sup> In a study of healthy volunteers, fentanyl produced muscular rigidity in 50%.<sup>20</sup> In the hospital surgical setting, such complications can be managed by trained personnel, intravenously administered muscle paralytics such as succinylcholine, and endotracheal intubation.<sup>1</sup> But for those taking F/FAs distant from a medically supervised situation, WCS can be a sudden and rapidly lethal complication. The critical point is that WCS differs fundamentally from opioid-induced respiratory depression.<sup>13,21</sup> And naloxone is poorly effective against F/FA-induced wooden chest syndrome.<sup>22</sup>

A synopsis of the relationship of WCS to overdose deaths:

- WCS is unique to F/FA and can occur at relatively low doses<sup>22</sup>
- WCS is an important factor in F/FA-related mortality<sup>21</sup>
- The ratio of emergency department (ED) admissions to deaths was 10:1 for heroin-related overdoses, but more fentanyl-related overdose deaths than ED visits were reported between 2015 and 2016.<sup>23</sup>
- In a study of 48 fentanyl deaths in one US county, nearly half of the cases had no detectable levels of norfentanyl, a major metabolite of fentanyl – suggesting a rapid death before the metabolite could be produced
- As a result, even in experienced (opioid-tolerant) opioid users, a small amount of fentanyl (1–2 ng/mL) can be lethal<sup>21</sup>

### 2.3 | What are the data regarding naloxone response success?

Naloxone is available in parenteral and intranasal formulations, has a relatively rapid onset of action (about 2 min) and has a duration of action of approximately 20–90 min.<sup>24</sup> Naloxone dosing is empirical – and depends on many factors related to characteristics of the drug, and of the affected individual. The recommended initial dose is 0.04 mg, increasing in increments if no response, to a maximum of 15 mg. Prior to F/FAs, unresponsiveness to 15 mg of naloxone was reason to surmise that it was not an opioid overdose.<sup>22</sup>

The data regarding response to naloxone in addressing F/FA overdose are somewhat obscured by the fact that even among

patients who are forthcoming about their drug use, may have taken F/FA unawares. However, there are data in overdose victims who likely did not consume F/FA. Several case studies prior to 2015 – when F/FA were not widely present in illegal drug products – show that naloxone was not always effective. In a retrospective study of consecutive cases where nebulized intranasal naloxone was used, 19% had no response to naloxone and the majority (59%) had only partial response.<sup>25</sup> In another study from the same time period, 16% required more than the 4 mg dose to be revived.<sup>26</sup> In a retrospective review of suspected opioid overdose in California, significantly more patients responded to combined routes of administration (intranasal followed by intravenous) than they did to one route alone.<sup>27</sup> And because of the short half-life of naloxone and other factors, revival from opioid-induced respiratory depression may be transient. In some cases, a continuous naloxone infusion is required.<sup>22</sup>

The current ubiquity of naloxone may create a false impression that it works equally effectively in all opioid-related overdoses, but, in reality, it has limitations with respect to overdoses of F/FA taken alone or in combination with other drugs.<sup>12</sup> Naloxone, a synthetic derivative of the MOR agonist oxymorphone, can antagonize opioid agonist-induced effects mediated by MOR, such as respiratory depression, and its high lipophilicity allows for its rapid entry into the brain.<sup>28</sup> Because it is a specific, high-affinity opioid antagonist that works by competing with the opioid agonist for MOR, naloxone has little activity in the body unless opioids are present.<sup>29</sup> It is thus considered safe to administer at doses as high as 24 mg/70 kg.<sup>29</sup> It does not effectively reverse overdoses caused by other drug classes, such as cocaine and alcohol.

In 2015, emergency medical services administered a mean total amount of 2.2 mg of naloxone and reversed toxicity in 94.2%, but by 2017 – when F/FA were becoming a greater fraction of opioid overdoses – the mean dose of naloxone increased by more than 50% to 3.63 mg, and the successful reversal rate dropped to 76.4%.

## 2.4 | Anatomy of an opioid overdose rescue

Resuscitation from an opioid overdose depends on numerous factors: the patient's overall health and degree of opioid tolerance, whether other drugs (particularly drugs that depress the central nervous system) have also been taken, the time interval between taking the drug(s) and the rescue, and the dose of the rescue agent. In contrast to the emergency due to an overdose of a typical opioid such as morphine, F/FA overdose has a faster onset, can progress to a fatal outcome more quickly, presents with atypical symptoms, and may or may not respond to naloxone.<sup>30</sup> When naloxone is used, larger amounts and multiple doses are often required.<sup>30,31</sup> In 2012, 14.5% of overdose patients required multiple naloxone doses, but by 2015, with the greater penetration of F/FA, the number rose to 18.2%. As F/FA use increased during COVID-19, this number is likely to increase even further.<sup>32</sup>

## 2.5 | Negative results of naloxone administration

If naloxone successfully competes with the opioid agonist at MOR, it will precipitate withdrawal symptoms (as a consequence of the phenomenon of physical dependence). It is not at all unusual for a person being treated for an opioid overdose with naloxone to emerge agitated, confused and even combative.<sup>29</sup> First responders who administer naloxone are often concerned about injury during the rescue, including physical assaults and needlesticks (and in the era of COVID-19, infection by the original coronavirus or a mutation of unknown virulence).<sup>29</sup> Polysubstance abusers who take opioids plus cocaine or other drugs can emerge from opioid-induced respiratory depression in a particularly highly agitated and hyperactive state. In a case series of EMS-treated overdose victims published in 2006 – when likely no F/FA was involved – 164 patients were treated on scene with naloxone.<sup>33</sup> Of this group, 22% died en route to the hospital. Of those who responded, 15% were agitated and combative and 4% suffered emesis.<sup>33</sup> While naloxone kits have been an effective harm reduction measure, it is increasingly recognized that the doses they offer may be inadequate to reverse an overdose involving F/FA.<sup>31</sup>

## 3 | WHAT IS NEW AND CONCLUSION

An overdose victim often cannot self-report what drug(s) were taken, and often the exact drug(s) ingested is not known. Many overdose victims are willingly or unknowingly consuming fentanyl or an illicit analogue. As more and more F/FA enter the street-drug stream, overdose mortality is rising and higher and more naloxone doses are needed. Naloxone is the only approved agent to reverse opioid toxicity. While it can in theory reverse opioid-associated mortality, F/FA also cause wooden chest syndrome, which can be fatal in a matter of minutes, and do not respond well to naloxone. Naloxone may be outmatched by ever-new and ever-more-potent F/FA. It might be necessary to explore alternative treatment strategies.

### ORCID

Robert B. Raffa  <https://orcid.org/0000-0002-1456-4451>

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