

Commentary: New Complications Make Treatment of “Opioid” Overdose Challenging

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Abstract

The “opioid crisis” has had a tremendous impact not only on its victims, but also on the practice of medicine, pain patients, and society in general. Unfortunately, efforts to “stem the tide” have not been successful at reducing overdose deaths. Counterbalancing the many ardent efforts to eliminate overdose deaths (such as the current widespread availability and use of opioid-receptor antagonists such as naloxone) is influx of the illicit fentanoids (*i.e.*, fentanyl and analogs). In addition to their high-potency, the fentanoids differ in surprising ways from more “traditional” opioids such as morphine and heroin. This uniqueness contributes to a reduced effectiveness of opioid receptor antagonists in the treatment of opioid overdose. Further greatly complicating overdose treatment is polysubstance abuse (e.g., an opioid plus a benzodiazepine). The non-opioid in the combination is not responsive to an opioid-receptor antagonist, which imparts additional challenges. Thus, the new reality introduces complications that negatively impact efforts to reverse “opioid” overdose. New approaches to improve outcomes in individuals who experience respiratory depression due to fentanyl-induced or polysubstance-induced overdose are needed. Approaches that harmonize with the new reality, perhaps something like a non-opioid “agnostic” pharmacologic ventilatory stimulant, would provide a welcome addition to the current choices.

Keywords

Opioid Overdose, Fentanyl, Naloxone, Polysubstance Abuse, Respiratory Stimulant

1. Introduction

The opioid crisis has profoundly impacted medical practice, pain patients, drug regulatory agencies, legislatures, insurers, the courts, and everyone else. The media, government, and professional organizations decried an over-prescription of, and near-unlimited access to, prescription opioid medications as the source of the problem [1]. Local, County, State, and Federal agencies developed regulations to “stem the tide” of prescription drug overdose [2]. Professional societies were formed to specifically combat the problem, and multiple guidelines were developed and promulgated [3] [4]. The concern was well-placed, but much re-primination and many good-intentioned efforts over-simplified the problem. While legislation and regulatory action was implemented, legal action and financial penalties enforced, professional societies swung the pendulum and become “anti-opioid”, overdose deaths continue to increase at a staggering rate [5] [6]. One of the issues is that the reality is changing. Prescription opioids are now a smaller part of the problem (Figure 1), replaced by illicit (and often adulterated) substances; low-potency opioids have been replaced by new high-potency opioids; and overdose is commonly poly-substance, *i.e.*, involves the combination of a non-opioid (such as a benzodiazepine) with the opioid. This new reality is unfortunately revealing an “Achilles heel” of the once nearly always effective opioid receptor antagonists (ORAs) such as naloxone. This is particularly unfortunate, given the recent trend to allow naloxone to be more accessible to patients, their family and other caregivers, and even school officials [7]. We present a succinct overview of the current problem, and speculate on what alternative mechanistic approach might augment the ORA approach.

2. The Complication of Fentanoids

Fentanyl was first synthesized and developed by Janssen Pharmaceutica in 1960 [8]. It was developed in order to overcome some of the disadvantages of morphine use in anesthesia. Fentanyl’s high potency, high lipid solubility, cardiostability, lack of propensity to cause histamine-release, and relatively short action, make it ideal for surgical anesthesia [9] [10]. Its physicochemical properties gives it the flexibility to be delivered by IV, SC, transdermal, transbuccal/mucosal, and intranasal routes [11]. Unfortunately, some of these same properties make the

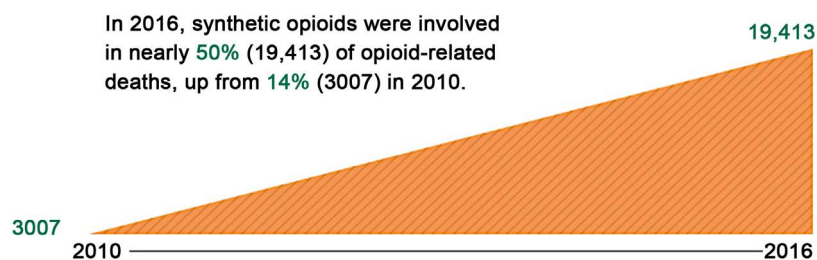


Figure 1. In 2016 synthetic opioids (primarily fentanyl) passed prescription opioids as the most common drugs involved in overdose deaths in the United States. <https://www.drugabuse.gov/sites/default/files/infographic-synthetic-opioids.pdf>

fentanoids (fentanyl and congeners), more “likeable” (Figure 2) [12].

Fentanoids have high binding affinity for the μ opioid receptor, and lower affinity for the δ - and κ -types [13]. They are more potent than morphine, meaning that a lower dose will provide the same level of effect as a higher dose of morphine. Members of the pharmaceutical fentanyl family (e.g., alfentanil, carfentanil, fentanyl, remifentanil, and sufentanil) are used in anesthesia and pain management. Illicitly-manufactured members of the fentanyl family, include illegal congeners (“designer” fentanoids). Multiple illicitly-manufactured fentanoids (IMFs) and “designer” fentanoids are readily available at low cost, often cheaper than alternatives [14].

Because of the physiochemical properties of the fentanyl’s, death can occur quickly (due to respiratory depression), especially in users who have not developed tolerance to opioids (actually, for reasons not understood there is very incomplete cross-tolerance between the fentanoids and other opioids) [15]. Whereas a heroin overdose causes death in about 30 minutes, a fentanyl overdose can cause death within only a very few minutes. The former timing provides a window of opportunity for intervention (administration of an ORA, for example), whereas the latter timing results in death before remedial action can be taken. Carfentanil is a fentanyl that is relatively easy and inexpensive to make and is much more potent than fentanyl [16]. It is both legally manufactured as an approved drug, and illegally made for abuse. It is only legally approved in the

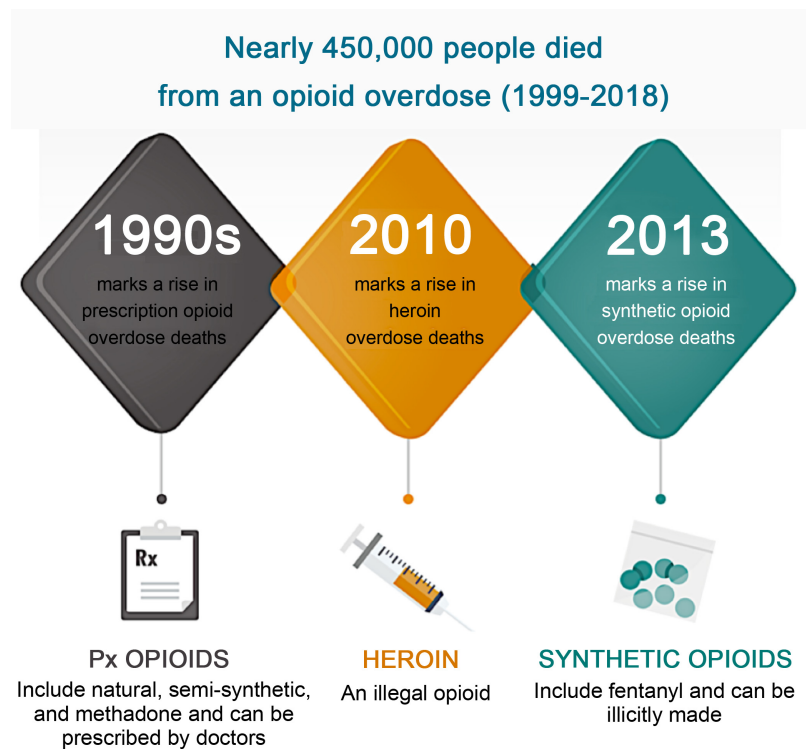


Figure 2. In 2016 synthetic opioids (primarily fentanyl) passed prescription opioids as the most common drugs involved in overdose deaths in the United States. <https://www.drugabuse.gov/sites/default/files/infographic-synthetic-opioids.pdf>.

US for veterinary practice. It has a very high binding affinity for the μ -opioid receptor, and has a potential for “re-narcotization”, which requires repeat dosing of an ORA to reverse. Fentanyl is approximately 50 to 100-times more potent than morphine; carfentanil is approximately 10,000-times more potent than morphine [14] [16]. It has been suggested that to treat a carfentanil overdose, “the initial naloxone dose administered should be greater than the maximum empiric naloxone dose recommended by the American Hospital Association” [16]. So it can be possible to reverse fentanoid-induced respiratory depression, even at high doses, but higher doses of the ORA are required, and for a longer time period (possibly even by continuous infusion) until the fentanoid is out of the system.

IMFs, produced in uncontrolled clandestine laboratories, is made from inexpensive and readily-available precursors, often using a fairly simple synthetic method [14]. IMFs are attractive because of high profitability. They are easy-availability on the Internet at a low price, and may escape detection in laboratory tests [14]. IMFs have been made into tablets resembling Xanax, Norco, and oxycodone, and added to cocaine and heroin [17].

3. The Complication of Atypical Effects of Fentanoids

Large doses of fentanyl can increase glucose and cause changes in both hippocampal and limbic temperature and metabolic activity [18]. These effects are different than those produced by morphine, heroin, or oxycodone. Amnestic syndromes are also seen with fentanyl overdose, but not with other opioids [19]. Many studies as well as clinical experience alert to cardiovascular complications with fentanyl overdose (including myocardial ischemia, QTc-prolongation and bradycardia), that could lead to fatal outcomes [20]. There have even been platelet effects reported for fentanyl [13]. Polysubstance use is a common finding with fentanoids: alcohol, benzodiazepines, and illicit substances [21]. Many individuals who overdose on these combinations often are unaware that a fentanoid was involved [8] [21]. Due to their high lipid solubility, fentanoids have different binding profiles at opioid receptors that modifies the “agonist:antagonist” ratio, impeding equilibrium competition, which may reduce the ability of naloxone to displace them [22].

4. The Complication of Polysubstance Overdose

Reports of polysubstance overdose deaths go back decades. A study of heroin overdose deaths in San Francisco in the 1970s found 47% positive for ethyl alcohol and 28% positive for “other drugs” [23]. Some estimates are as high as 80% [24], involving alcohol, sedatives, benzodiazepines, and illicit drugs [25] [26]. For example, ethanol together with oxycodone causes greater ventilatory depression than does either alone [27]. Benzodiazepines are one of the most commonly-prescribed substances [28], and they are often implicated in opioid-related deaths [29]. Other frequent combinations involve cannabis/cannabi-

noids, cocaine, and amphetamines [30] [31] [32] [33], although the estimates are highly variable [33]. Those who abuse fentanoids tend to display greater poly-substance abuse, although this may be due to secondary factors such as greater availability, lower cost, or being unaware of the composition of what is being taken [8] [13]. There is also lack of consensus concerning aspects of the appropriate forensic and medico-legal determination of fentanoid overdose death. Even the appropriate site of specimen collection is “still under debate” [34].

5. The Complication of Naloxone vs Fentanyl and Fentanoids

It has been reported that “respiratory depression by fentanoids is harder to reverse with naloxone ... and may require multiple and/or higher doses of naloxone.” [22]. For other opioids, it used to be common practice to keep the naloxone dose low in order to prevent serious problems with acute precipitated withdrawal. However, a requirement for higher doses of naloxone have become the norm in today’s IMF environment. The use of higher doses and multiple doses of naloxone depend of a number of criteria, including regional differences, type of fentanoid and other drugs that are on board. Therefore, it is difficult to establish a “standard” naloxone dosage and dosing schedule in a given overdose setting [35]. Fentanyl use, especially intravenously, has a higher incidence of overdose compared to other opioids. The risk is twice that of heroin, and 8-fold that of oxycodone or morphine [14]. This might result from the fact that fentanoids display “atypical micro-pharmacokinetics” that could affect how naloxone acts at the opioid receptor [22], reducing the ability of naloxone to displace a fentanoid from the receptor [22].

Opioid-induced chest wall rigidity, also called “WoodenChest Syndrome (WCS)”, has been known for decades, although it is usually described in the anesthesiology literature related to surgical procedures [8] [36]. WCS presents as muscle-wall rigidity, laryngospasm, seizure-like events, cyanosis, and loss of consciousness [37] [38]. WCS related to overdose has become more common as the use of illicit fentanoids has increased. WCS can be seen with as little as 50 micrograms of intravenous fentanyl [8]. The incidence has been reported to be anywhere from 8% to 100%, and has also been reported for alfentanil, norfentanyl, and sufentanil [39] [40]. Overdose death from fentanyl can occur so quickly that a metabolite, norfentanyl, is often not found in toxicologic examination [39]. This has been used as support for the argument that WCS is a cause of fentanoid-induced respiratory depression and overdose death. Not only is WCS not reversed by an ORA—an ORA may make it worse [36]. It has been suggested that fentanoid overdose sets up a potential “double-whammy”: WCS and respiratory depression [22]. Recent data suggest that perhaps it is a “triple-whammy”: WCS, respiratory depression, and laryngeal spasm. There have been suggestions that WCS is either caused by, or is exacerbated by, naloxone [41]. The mechanism and actual incidence are not known, nor has a clear treatment paradigm been developed [42]. But laryngospasm is almost exclusively reported with lipophilic opio-

ids, such as the fentanoids [36]. Fentanoids increase norepinephrine levels, which can worsen both chest wall rigidity and laryngospasm [38]. Activation of the recurrent laryngeal and external superior laryngeal nerves are stimulated by sympathetic innervation and norepinephrine release [38]. Motor neurons involved in laryngeal function increase their firing rate within 20 secs of an intravenous fentanyl injection [43]. The stimulation of norepinephrine release by fentanyl is intensified by the blockade of locus coeruleus GABAergic inhibitory neurons [44]. Cholinergic stimulation by fentanyl may also cause reduced perfusion on coronary, hepatic and cerebral systems [40]. This might explain the chest pain and bradycardia seen in fentanyl overdose [44].

Unlike morphine or oxycodone, which in low to moderate doses increases brain oxygen levels through neurovascular compensation, fentanyl produces a dramatic reduction in brain oxygen levels [36]. Fentanyl is 10 to 20-times more potent in this reduction than is morphine [38]. When fentanyl is used with heroin, the combination produces an even greater reduction in brain oxygen levels [38]. And unlike other opioids, fentanyl reduces both tidal volume and respiratory rate [15].

6. Looking Ahead: Respiratory Stimulants?

Since analeptics (central nervous system stimulants) have a long history, but recently there has been a renewed interest as an addition to ORA treatment of drug overdose. Although various agents have been used for decades to stimulate respiration, most of them were used in the surgical suite, had significant side effects, and are no longer used. But due to the conundrum prompted by the popularity of illicit fentanoids and polysubstance abuse, there is a need for alternatives and additives to the apparently diminishingly-effective ORAs. As a result, there has been a resumed interest in respiratory stimulation as a strategy. Such an agent would be “agnostic” to the type of drug inducing the respiratory depression. A number of agents have been, or are being, evaluated. These include modulators of some potassium channel subtypes, serotonin receptor agonists, agents that interact with ionotropic AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) subtype of glutamate receptor (AMPAkinases), and phosphodiesterase inhibitors [45].

Almitrine, (2,4-Bis(allylamino)-6-[4-[bis(p-fluorophenyl)methyl]-1-piperazinyl]-s-triazine), is an older drug that was shown to produce short-term improvements of respiration in patients with acute respiratory failure [46]. Although it was never approved in the US, and it was removed from the European market due to weight loss and peripheral neuropathy with chronic administration, its mechanism of action is informative. It acts as an agonist at peripheral chemoreceptors expressed on carotid bodies. Its site of action was demonstrated when transection of the carotid sinus nerve blocked the ventilatory effects of almitrine [47]. More specifically, almitrine inhibits Ca^{2+} -dependent K^+ channels without altering voltage-dependent K^+ , Na^+ , or calcium currents [48].

Doxapram, 1-Ethyl-4-(2-morpholin-4-ylethyl)-3,3-diphenyl-pyrrolidin-2-one, was developed in the 1960s, and is still available for use as an analeptic respiratory stimulant [49]. Precautions are needed for certain patient populations [50]. Doxapram is a potent inhibitor of TWIK (Tandem of P-domains in a Weakly Inward rectifying K⁺ channel)-related acid-sensitive K⁺-channels (TASK-1 and TASK-3) with an action on the carotid body [49] [51].

ENA-001 (formerly GAL-021), 2-[(*N*-Methyl-*N*-methoxyamino)]-4,6-bis(propylamino)-1,3,5-triazine, also acts on select potassium channels in the carotid body, but in a different way, and on a different part of the homeostatic feedback loop than does almitrine and doxapram. It inhibits large-conductance Ca²⁺/voltage-activated K⁺ channels, BK_{Ca} (also known as Maxi-K, KCNMA1, Slo1), primarily working through the carotid body [52] [53]. In human volunteers under isohypercapnic conditions, a separation between ENA-001 and placebo on minute ventilation was observed at low-dose alfentanil plus high-dose ENA-001 and high-dose-alfentanil plus high-dose ENA-001. Similar observations were made on poikilocapnic ventilation and arterial pCO₂ [54].

7. Conclusions

The current climate of fentanyl overdose presents significant complications for successful treatment, partly because fentanoids have unique features different from other opioids that are abused. Some known and suspected differences include:

- Higher potency,
- Faster onset,
- Complex competition with naloxone at the opioid receptor,
- Changes in brain glucose levels and temperature,
- Cardiovascular effects,
- Wooden chest syndrome,
- Laryngeal spasm,
- Reduced brain oxygenation.

These all may contribute to fentanyl-induced deaths and the resistance seen to standard receptor-antagonist therapies such as naloxone. These cases are further complicated by the common occurrence of polypharmacy. They can be very complicated and require close monitoring and aggressive treatment.

With other, even more highly potent, fentanoids on the horizon [55], there is a need for additional therapies with novel mechanisms of action that could supplement efforts to reverse acute respiratory depression. Naloxone will not likely be replaced in the near future, but, unfortunately, in spite of its increased use and availability, alone this treatment may not be enough. The use of non-opioid derived medications, such as respiratory stimulants, might be a welcome possible new approach.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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