# Reversal of high potency synthetic opioid overdose: literature review.

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*The views expressed are those of the authors and do not represent the official position of the US Food and Drug Administration.*

## Abstract

Opioid misuse and abuse have long been public health issues in the United States, but recent increases in overdose-related deaths caused the U.S. Department of Health and Human Services to declare the opioid crisis a national public health emergency. The purpose of this project was to evaluate the landscape of available information and scientific considerations surrounding intranasal, intramuscular, and intravenous routes of opioid antagonist development addressing prescription opioid overdose reversal, and illicit highly potent opioid overdose reversal. A literature search of the PubMed database was conducted using keywords in order to review historical and current scientific knowledge of synthetic opioid overdose reversal. Additionally, publicly available regulatory documents were evaluated from the websites of CDC, DEA, FDA, NIDA, and the Federal Register. In vitro binding data at the μ-opioid receptor suggest carfentanil, a veterinary tranquilizer, has the highest affinity. Pharmacokinetic and pharmacodynamic data regarding illicit highly potent synthetic opioids are uncharacterized, making it difficult to determine the most appropriate reversal therapy. However, pharmacokinetics of fentanyl, a synthetic prescription opioid, and its pharmacodynamic effects on respiration have been characterized over the last several decades, which could serve as a model. Additionally, pharmacodynamics of opioid antagonists such as naloxone and nalmefene on fentanyl-induced respiratory depression are described in the literature. Nalmefene is labeled to be effective in reversing fentanyl's respiratory effects when administered perioperatively. A preclinical study in African green monkeys suggests naloxone may be able to protect against carfentanil overdose. Effects of carfentanil, considered to be the most potent synthetic opioid currently known, were reversed with IV bolus naloxone. After carfentanil administration, nalmefene and naloxone block its effects. Using these limited data, model-informed drug development (MIDD) can play an important role in future research towards better antagonist development and application. We identify knowledge gaps in science of opioid overdose reversal that need to be addressed for successful development of therapies.

## Methods

PubMed database was searched using specific key words and phrases, alone and in strategic combinations, along with data constraints to understand development of scientific knowledge over time.

Examples:

- "synthetic opioid" in each decade
- "prescription opioid binding"
- "illicit opioid binding"
- "opioid overdose reversal"
- "non-pharmaceutical fentanyl"
- "mu opioid receptor antagonist"
- "opioid antagonist binding"
- "high potency opioid"

- Drugs@FDA was utilized to access information about approved opioid agonists and antagonists, including labeling and reviews made public under the Freedom of Information Act
- FDA Human Drug Advisory Committee Meeting documents relevant to opioid agonists and antagonists and publicly available at FDA.gov were accessed and evaluated
- CDC and DEA databases were accessed for data regarding illicit opioid use and overdose reports

## Results and Discussion

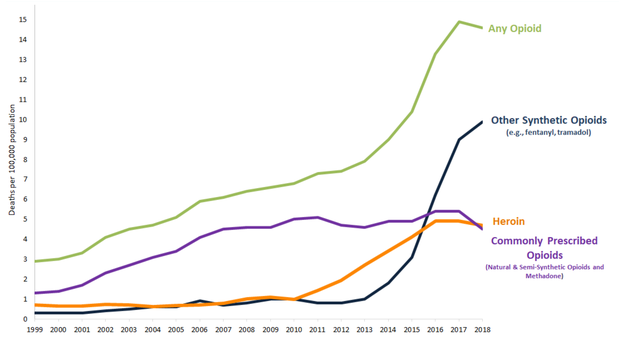


**Figure 1.** Overdose Deaths Involving Opioids, by Type, United States, 1999-2018.[1]

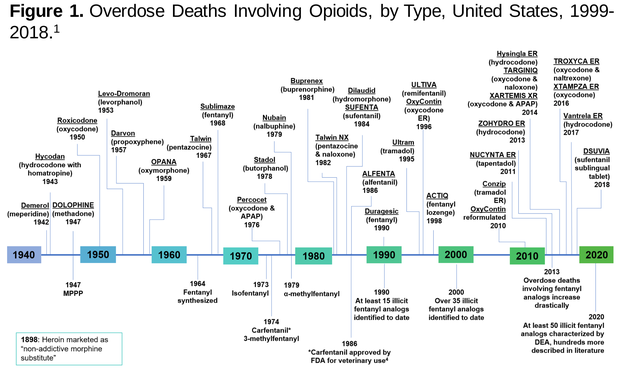


**Figure 2.** Timeline of FDA-approved opioid agonists.

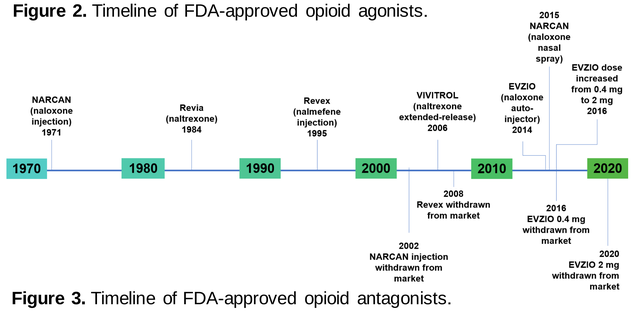


**Figure 3.** Timeline of FDA-approved opioid antagonists.

| Drug | $k_{on}$ ($\mu mol^{-1}min^{-1}$) | $k_{off}$ ($min^{-1}$) | $t_{½}$ (min) | $K_i$ (nM) |
|---|---|---|---|---|
| Naloxone | 47 ± 21 | 0.85 ± 0.33 | 0.82 | 18 |
| Naltrexone | 100 ± 57 | 0.35 ± 0.091 | 2.0 | 3.5 |
| Nalmefene | 58 ± 23 | 0.29 ± 0.10 | 2.4 | 5.0 |

**Table 1.** Mu-opioid receptor binding parameters in vivo of opioid antagonists.[2]

| Compound | $K_i$ (nM) | $EC_{50}$ (nM) | Compound | $K_i$ (nM) | $EC_{50}$ (nM) |
|---|---|---|---|---|---|
| Fentanyl | 1.6 | 0.51 | Fentanyl | 1.6 | 0.51 |
| Morphine | 4.2 | 50-100 | Morphine | 4.2 | 50-100 |
| Carfentanil | 0.024 | 0.006 | Cyclobutylfentanyl | 5 | 160 |
| cis-3-Methylfentanyl | 0.32 | 4.2 | p-Methylfentanyl | 5.5 | 450 |
| o-Fluorofentanyl | 0.4 | 15 | β-Hydroxythiofentanyl | 6.2 | 138 |
| o-Fluorobutyrylfentanyl | 0.7 | 60 | Cyclopentylfentanyl | 6.6 | 600 |
| o-Fluoroacrylfentanyl | 1.1 | 14 | Isobutyrylfentanyl | 6.6 | 137 |
| trans-3-Methylfentanyl | 1.1 | 25 | p-Methylcyclopropylfentanyl | 7.2 | >1000 |
| Furanylfentanyl | 1.3 | 9.3 | Furanylethylfentanyl | 8 | 350 |
| o-Fluoroisobutyrylfentanyl | 1.3 | 42 | p-Fluorofentanyl | 10 | 164 |
| Acrylfentanyl | 2.1 | 68 | β-Methylfentanyl | 14 | >500 |
| Cyclopropylfentanyl | 2.4 | 55 | Methoxyacetylfentanyl | 17 | >500 |
| o-Methylfentanyl | 3.4 | 58 | α-Methylacetylfentanyl | 19 | >500 |
| Butyrylfentanyl | 3.5 | 80 | m-Fluoroisobutyrylfentanyl | 24 | >1000 |
| m-Fluorofentanyl | 4.2 | 79 | Tetrahydrofuranfentanyl | 31 | 390 |
| m-Methylfentanyl | 4.2 | >1000 | o-Methylacetylfentanyl | 43 | >1000 |
| p-Fluoroacrylfentanyl | 4.3 | 84 | p-Chlorofentanyl | 45 | >1000 |
| p-Fluoroisobutyrylfentanyl | 4.5 | >500 | Acetylfentanyl | 64 | >2000 |

**Table 2.** Mu-opioid receptor binding affinity ($K_i$) and potency ($EC_{50}$) in vitro of illicit opioid agonists.[3]

- Carfentanil is approximately 10,000 times as potent as morphine and is considered the most potent fentanyl analog currently known
- Advances in binding study technology in the 1980s allowed visualization of human opioid receptors for the first time via PET imaging; this led to important advances in understanding of binding
- Effects of radiolabeled [$^{11}$C]carfentanil were studied in healthy subjects at doses of approximately 4.6 – 6.9 μg with and without naloxone 1 mg/kg
- IV bolus naloxone 1 mg/kg blocked all subjective effects of carfentanil

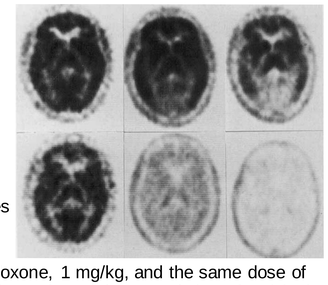

**Figure 4.** Localization of opiate receptors in man using [$^{11}$C]carfentanil. Images in the top row were obtained using the Neuro ECAT from 30-60 min after IV administration of 25 mCi [$^{11}$C]carfentanil, 80 ng/kg. Images were localized using X-ray CT at approximately 7.2, 4, and 0.8 cm above the canthomeatal line. Images in the bottom row were acquired at the same time following IV administration of the opiate antagonist naloxone, 1 mg/kg, and the same dose of [$^{11}$C]carfentanil used in the first study. Preferential accumulation of activity is seen in areas known to contain high concentrations of opiate receptors while low activity is seen where opiate receptors exist in low concentrations. The images in the bottom row demonstrate the low level of nonreceptor binding in the brain and pituitary gland.[4]

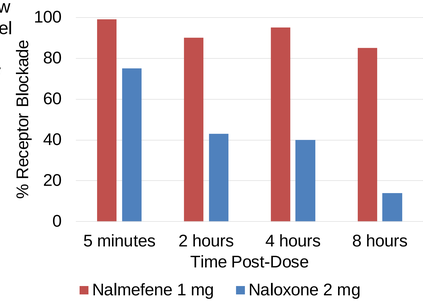


**Figure 5.** Mean receptor blockade of nalmefene 1 mg vs. naloxone 2 mg in four subjects evaluated by PET using [$^{11}$C]carfentanil.[5]

## Conclusion

### Knowledge Gaps

- Most appropriate course of treatment for known and suspected high potency synthetic opioid overdose
- PK and PD data regarding high potency synthetic opioids and ability to determine these data from in vitro and in vivo studies
- Clinical translation of tracer dose radioligand binding studies (e.g., [$^{11}$C]carfentanil imaged with PET) to overdose levels
- In vitro and in vivo binding study translation to clinical effects (e.g., analgesia, respiratory depression, sedation, nausea/vomiting, etc.)
- Plasma concentrations of illicit opioids after administration

### New Frontiers in Overdose Reversal Research

- Altered naloxone dosing guidelines - should a higher dose of naloxone be administered in the event of known or suspected opioid overdose?[6]
- New antagonist compounds (e.g., methocinnamox, naltrexone-14-O-sulfate)[6,7]
- New formulations/administration routes of existing compounds (e.g., intranasal nalmefene)[6]
- Implantable device for high-risk individuals that automatically releases naloxone when respiratory depression is detected[8]

### Project Summary

- The use of the term "synthetic opioids" has changed over time, shifting from widespread use regarding prescription opioids with synthetic origin to frequent reference of illicit high potency synthetic opioids
- The use and nontherapeutic use of illicit high potency opioids have increased dramatically over the past 20 years, with overdose trends following suit
- PK and PD data are available regarding the efficacy of naloxone, naltrexone, and nalmefene in reversal of prescription opioid overdose, but little is known about application to reversal of illicit high potency synthetic opioids
- Little data is available regarding PK or PD of illicit fentanyl analogs and translational mechanisms from preclinical studies are not well-defined
- MIDD can play an important role in future research to help identify appropriate regimens to reverse different opioids and to understand the time course of respiratory depression recovery
- Structure-activity relationship studies have provided some insight into binding affinity of some fentanyl derivatives, but translational utility has not yet been determined[9]

## References

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