# Demonstrating Efficacy When Clinical Trials Are Impossible: QSP Modeling to Support a New Dose Application

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# Clinical trials are not always the solution.

- The US is currently in a drug overdose epidemic
  - The majority of overdose deaths involve opioids, particularly synthetic opioids (such as illicitly-made fentanyl) combined with other drugs
  - Naloxone can be used to reverse an opioid overdose, but there are questions about the dose needed for synthetic opioids
- Clinical trials on overdose subjects would be unethical and impractical
- Pharmacological modeling can be used to supplement regulatory submissions when clinical trial data is not possible
- This webinar discusses the development of a mathematical model of the opioid mu receptor occupancy of fentanyl and naloxone to support a regulatory submission

# Agenda

- Background on Fentanyl and Naloxone
- Opioid Epidemic
- Modeling Mu Receptor Dynamics
- Results and Conclusions
- How Were the Modeling Insights Used?

# Background on Fentanyl and Naloxone

## Fentanyl

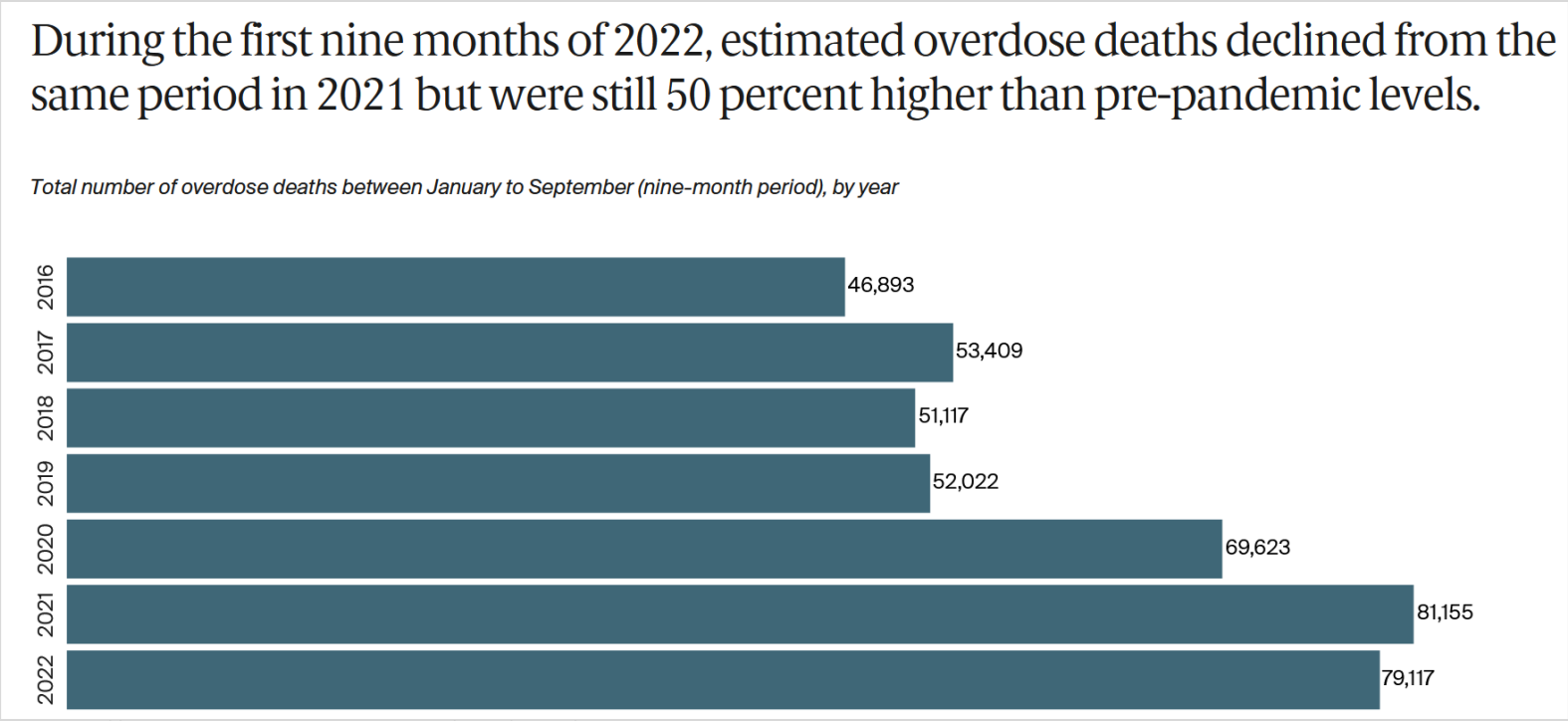
- Mu receptor agonist
- Synthesized in 1960
- FDA approval in 1972
- Initially used in anesthesia, then pain
- Transdermal patch approved 1990
- Abuse of patch warning in 1994
- Beginning of current epidemic 2013
- Opioids involved >66% of OD in 2021*
- Fentanyl pharmacology: 18,365 papers on PubMed

## Naloxone

- Mu receptor antagonist
- Synthesized in 1960
- FDA approval in 1971
- Used to reverse opioid overdose
- Pilot take-home kits tested in 1996
- Nasal spray approved by FDA 2015
- Take-home kits are now common
- Naloxone pharmacology: 29,598 papers on PubMed

Both drugs have 63 years of pharmacology studies

# The Current Opioid Epidemic

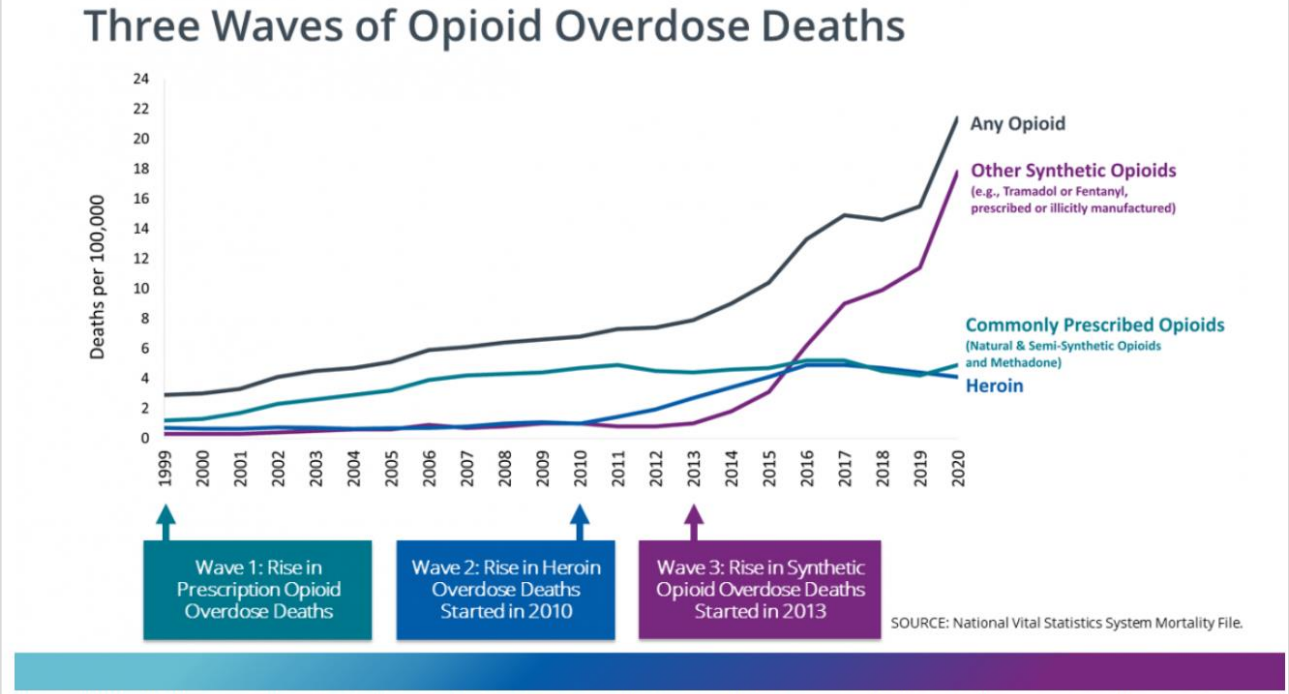



https://www.commonwealthfund.org/blog/2023/overdose-deaths-declined-remained-near-record-levels-during-first-nine-months-2022-states#:~:text=An%20estimated%2079%2C117%20Americans%20died,higher%20than%20pre%2D2020%20levels.

- The CDC has attributed the largest increase in deaths to illicitly manufactured synthetic opioids, such as fentanyl and its derivatives
  - https://www.cdc.gov/opioids/basics/epidemic.html

*Moss 2019 PMID: 30777088

# The opioid epidemic has occurred in waves.




From 1999–2020, more than 564,000 people died from an overdose involving any opioid, including prescription and illicit opioids[1].

- Current wave is driven by very potent synthetic opioids
- Overdose trends involving prescription opioids or heroin have stabilized or declined
  - https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates

# We hypothesize that higher doses of naloxone are needed to combat this trend of overdoses.

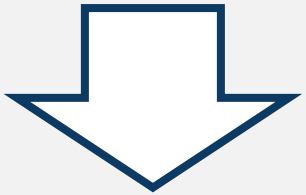
- Associated with the dramatic increase in deaths due to fentanyl overdoses have been resuscitations requiring multiple doses of naloxone at approved doses (2 mg intramuscular (IM) or 4 mg intranasal (IN))
  - Fentanyl is considered 100 times more potent than morphine*
  - Other synthetic opioids are even more potent*
  - Receptor occupancy by fentanyl and the ability of naloxone to displace this opioid are key factors in reversing opioid toxicity
- Zimhi, a 5 mg naloxone IM injection, was going for 505(b)(2) approval to the FDA


Zimhi 5 mg naloxone injection

**Regul Toxicol Pharmacol.* 2011;59(3):385-390.

# How do you show the utility of a new dose without a clinical trial?

**Naloxone Clinical Trials in Overdose Subjects**

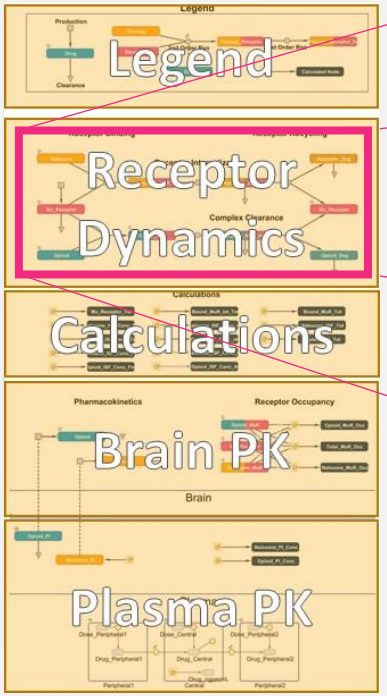


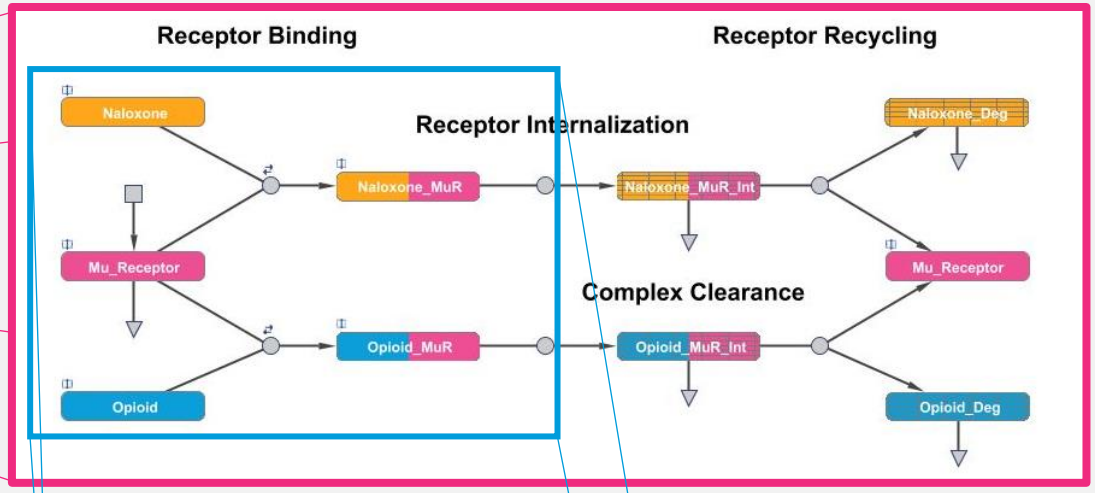
**Mathematical Modeling to the Rescue!**

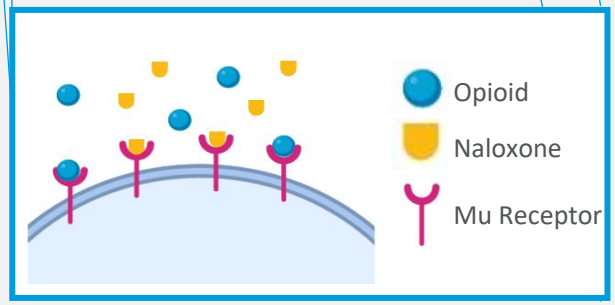
1. Model the opioid mu receptor occupancy with fentanyl
2. Give different doses of naloxone
3. Evaluate the hypothesis that higher doses of naloxone are beneficial

# Fentanyl and Naloxone Compete for Mu Receptor

Model developed in MATLAB® SimBiology®




Competitive Receptor Binding Depends on:

- Ligand Concentrations
- $K_{on}$, $K_{off}$

- The Model includes plasma and brain pharmacokinetics and mu receptor dynamics
- It can simulate the dynamics of:
  - Fentanyl concentration in plasma and brain
  - Naloxone concentration in plasma and brain
  - Competitive receptor binding

# Considerations for Model Development

| Knowledge and Data | | Effect on Modeling |
|---|---|---|
| Minimal clinical trial data due to ethical considerations | → | Utilize modeling to support dose and receptor binding data |
| No control over fentanyl dosage and route with multiple routes possible: intravenous, intranasal, intramuscular, transdermal, oral, sublingual, subcutaneous, rectal | → | Start simulations at a specific blood concentration. Assumes that no additional fentanyl is absorbed or taken after that time. |
| Time of fentanyl administration and time until naloxone administration are unknown | → | Start simulations at a specific fentanyl blood concentration. Assume naloxone is given at the time that the fentanyl concentration was reached, i.e., time 0. |
| Naloxone administered by community or EMS personnel | → | Single dose of naloxone given, no additional medication administered |

# Key Modeling Approaches and Assumptions

- Median reported binding affinity values of naloxone and fentanyl to mu receptors were used
  - The literature reports a wide range of binding affinities for each of these drugs

- Brain PK was inferred based on relevant data, including receptor occupancy, binding affinity, and duration of clinical effects
  - Transport kinetics of naloxone and fentanyl from plasma to the brain is insufficiently characterized to be modeled mechanistically
  - Brain PK for fentanyl in particular is inconsistent with plasma PK (plasma half-life vs. actual symptom duration) suggesting complex transport and/or non-specific binding mechanisms

- Mu receptor dynamics (synthesis, degradation, internalization, recycling) were set assuming a chronic opioid user with delayed receptor recycling

# Peak fentanyl concentration depends on the dose and route of administration.

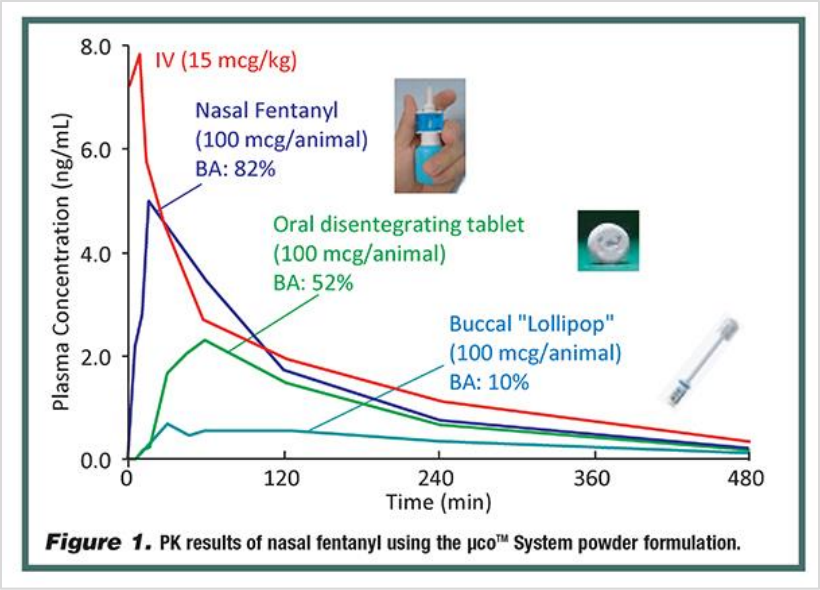
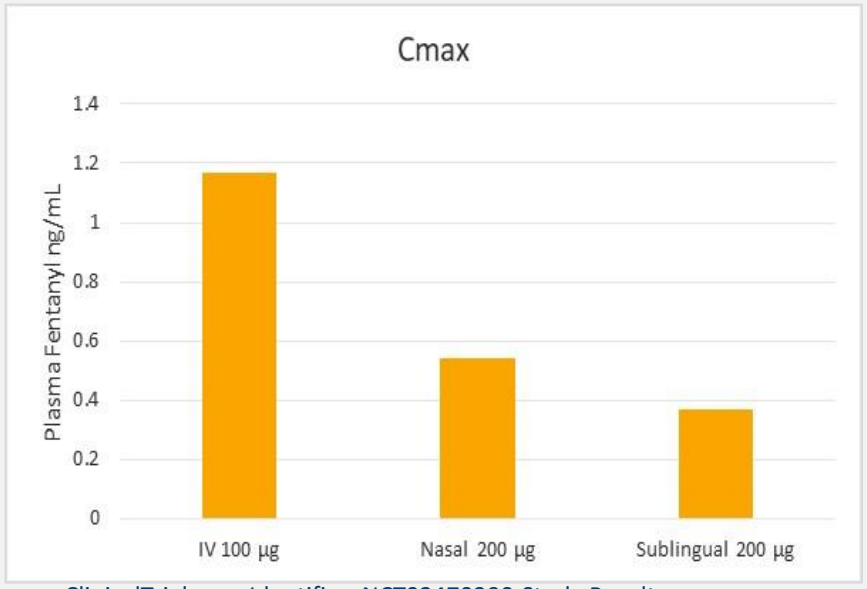



***Figure 1.*** **PK results of nasal fentanyl using the µco™ System powder formulation.**

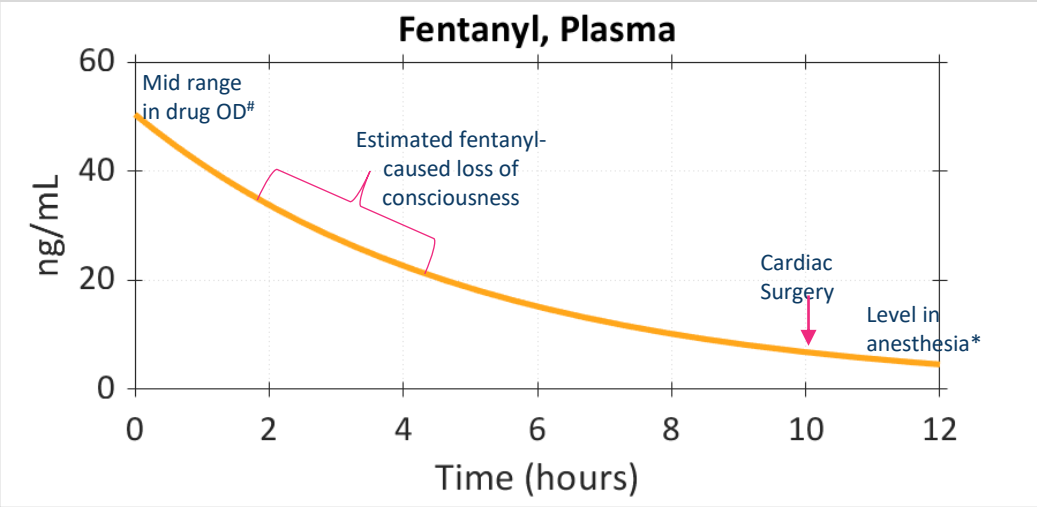
https://drug-dev.com/pain-management-rapid-action-therapy-in-pain-relief-potential-for-nasal-delivery-systems/

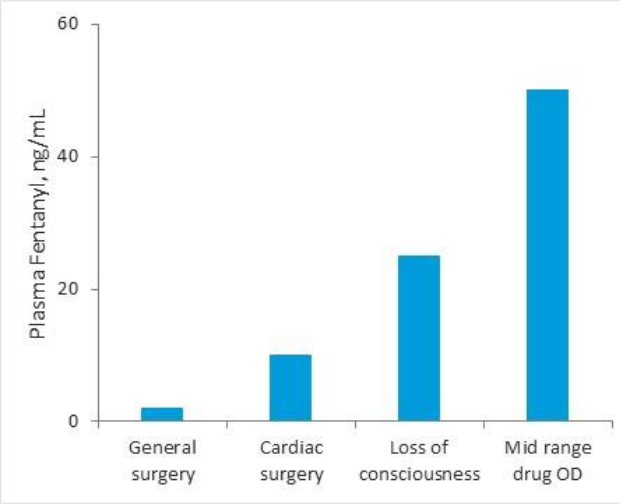



ClinicalTrials.gov Identifier: NCT02470390 Study Results

- Cmax of fentanyl is determined by bioavailability and absorption rate
  - Intranasal bioavailability is 55-75% (Paech 2003 PMID: 12859464)
  - Buccal bioavailability is 30-50% (Lötsch 2013 PMID: 23100195, Darwish 2007 PMID: 17322146)
- The Opioid Platform focuses on post-Cmax concentrations

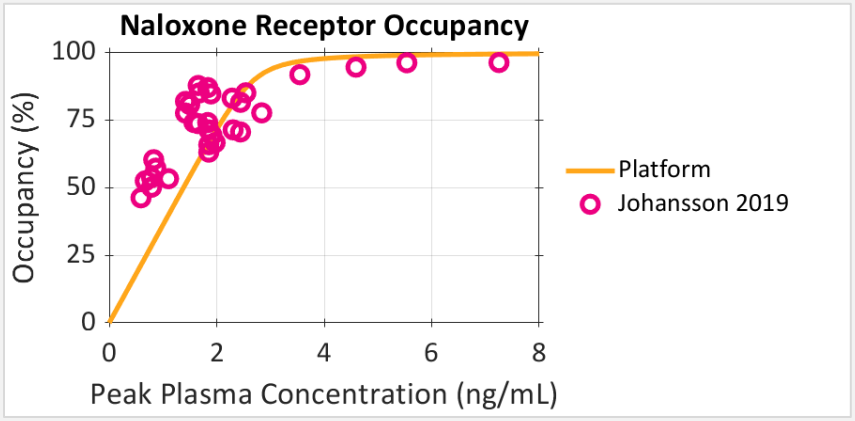
# Simulated fentanyl concentration corresponds to overdose level.

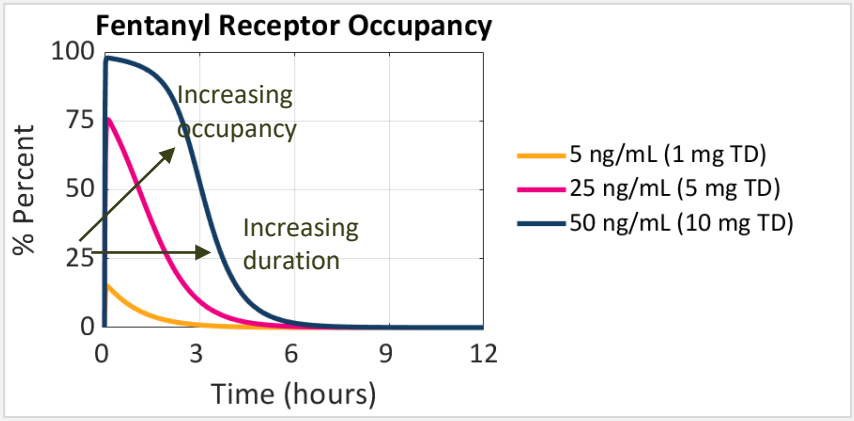



- Fentanyl plasma PK is simulated from the plasma peak concentration (Cmax) of 50 ng/mL consistent with overdose levels seen in patients
  - Implementation does not depend on the route of administration
- Fentanyl plasma half-life is ~3.5 hours (Corli and Roberto 2014 PMID: 24346227)

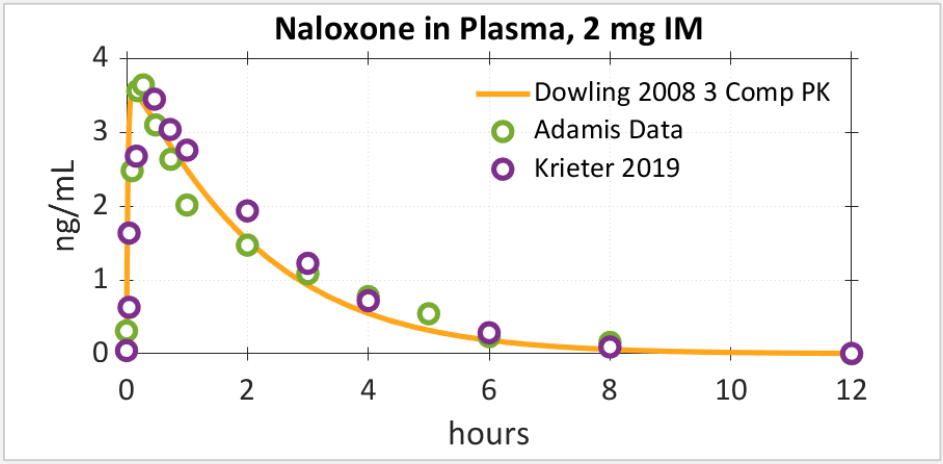
# Key Validation Points of Model

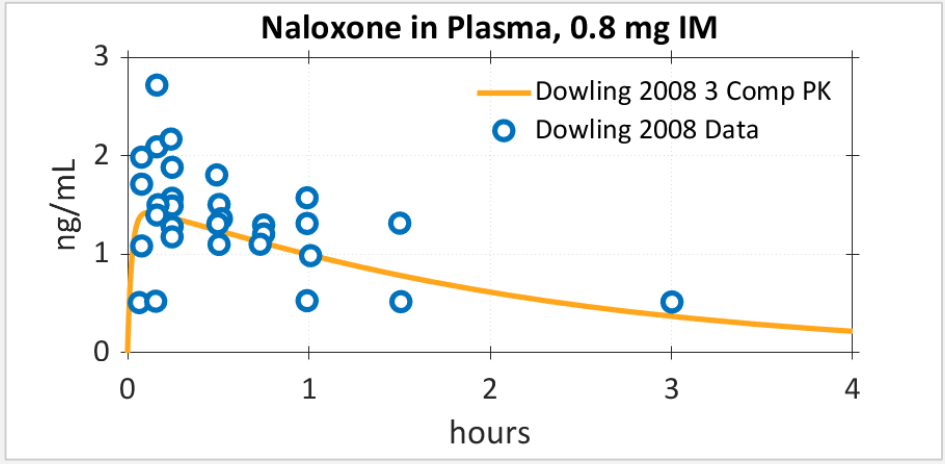



- Naloxone receptor occupancy (left) increases as naloxone dose increases, consistent with data from Johansson 2019 PMID: 30867551
- Fentanyl receptor occupancy (right) dose-response and duration is consistent with reported therapeutic ranges and symptoms
  - (Dahan 2005 PMID: 15833777, Foster 2008 PMID: 18728103, Bovill 1980 PMID: 7426257, Takahashi 2004 PMID:14991468)

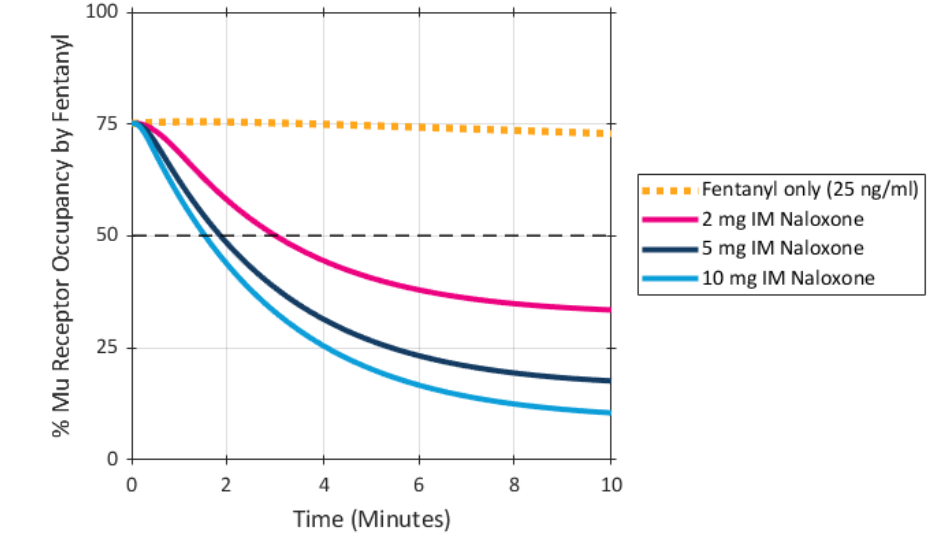
# The simulated naloxone plasma PK was in good agreement with the available data.



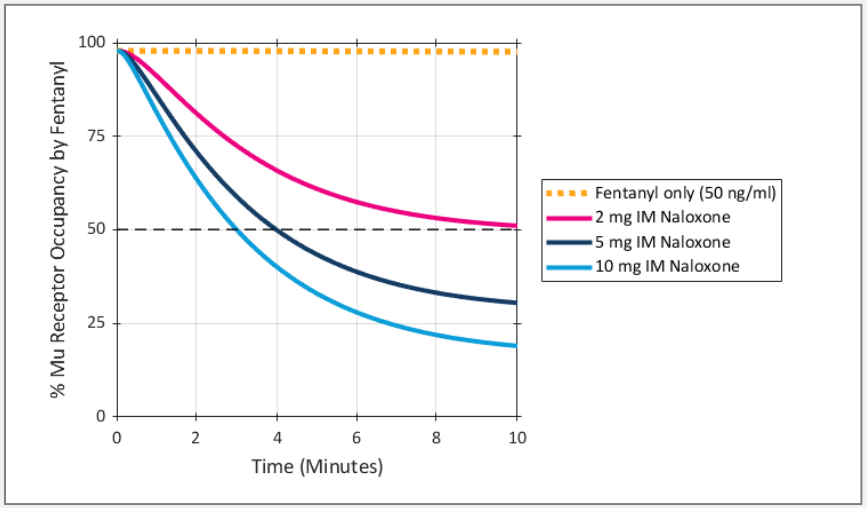

- Naloxone 3 compartment PK model for intramuscular (IM administration) from Dowling 2008 PMID: 18641540 was implemented in the Platform
- This PK model captures both data provided by the client and literature data (Krieter 2019 PMID: 30861160, Dowling 2008 PMID: 18641540)
- Simulation Protocol:
  - 2 mg (left) or 0.8 mg (right) single dose of naloxone are administered at the start of the simulation
  - Platform is run for a 12 hour simulation

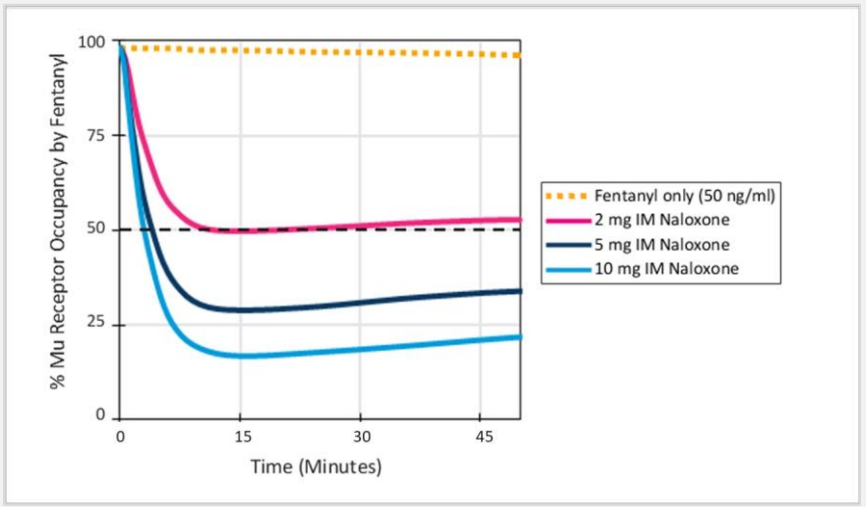
# Results: 25 ng/ml Fentanyl, Naloxone Dose Response




- We assume a peak fentanyl plasma concentration of 25 ng/mL (~5 mg dose of fentanyl TD), corresponding to ~75% receptor occupancy (RO) by fentanyl
- 50% mu RO (dashed black line) is generally considered the point at which the patient loses the ability to breathe
- Naloxone 2, 5 and 10 mg doses (IM) were administered at time 0
- All tested naloxone doses reduced RO by fentanyl to below 50% within 10 minutes
- Higher doses of naloxone achieved the reduction below 50% faster

# Higher doses of naloxone reduce receptor occupancy below 50% and limit renarcotization.

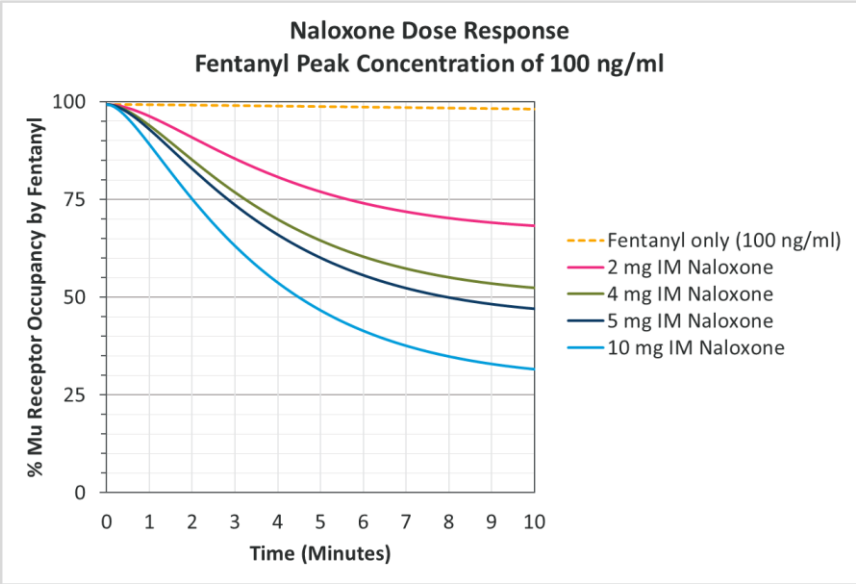


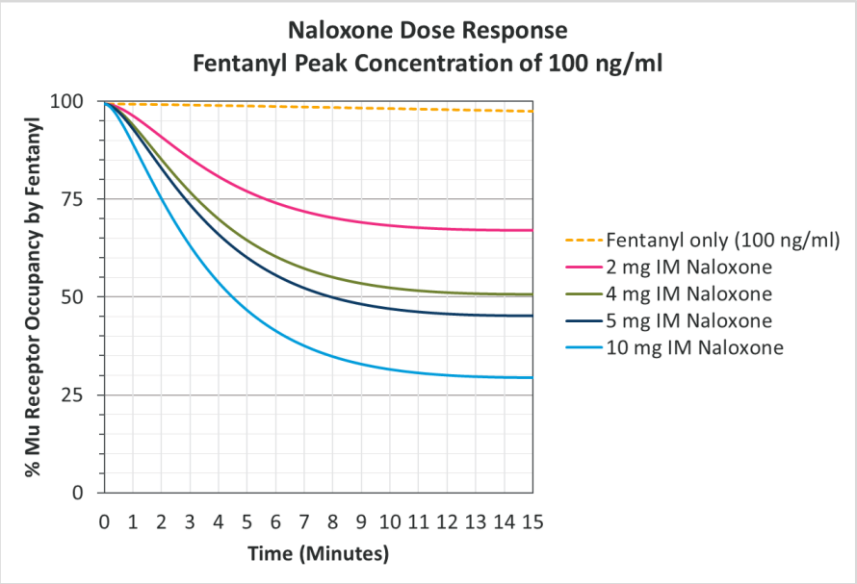




- Fentanyl at 50 ng/ml is a median overdose concentration*
- Higher doses of naloxone reduce mu RO by fentanyl faster and to a greater extent than the currently approved 2 mg IM dose
- Renarcotization can be seen for the 2 mg dose of naloxone as fentanyl RO increases above 50% over time (right)

*Gill 2013 PMID: 22890811

# Results: 100 ng/ml Fentanyl, Naloxone Dose Response




- Naloxone 2, 4, 5 and 10 mg doses (IM) were administered 5 minutes after a peak fentanyl plasma concentration of 100 ng/mL (~20 mg dose of fentanyl)
- After 10 or 15 min, 2 and 4 mg doses of naloxone were not able to achieve RO < 50%

# Conclusions of Mu Receptor Occupancy Model

- Assuming a typical fentanyl overdose concentration of 50 ng/ml, mu receptor occupancy by fentanyl is about 98%
- 10 minutes after naloxone administration at 2, 5, or 10 mg (IM) RO was estimated to be 50%, 29%, or 17%
  - 2 mg dose just barely reaches the 50% RO threshold to restore the patient's breathing
- The time to drop below 50% fentanyl RO given 2, 5, or 10 mg (IM) of naloxone was estimated to be 10 minutes, 4 minutes, and 3 minutes, respectively
- Higher concentrations of fentanyl require higher doses of naloxone for effective reversal
- Lowering fentanyl binding during the first 15 minutes by using higher doses of naloxone may result in more rapid and successful reversal of opioid toxicity and decrease mortality from this potent opioid

# Overall Conclusions

- Higher naloxone doses are predicted to safely reverse more opioid overdoses and save lives
- Simulations using the opioid receptor model demonstrate the utility of higher naloxone doses in displacing fentanyl from the mu receptor
- Naloxone at 5 or 10 mg reduced fentanyl receptor occupancy below 50% level for a longer time than the 2 mg dose at
- At higher levels of fentanyl, naloxone at 5 or 10 mg was necessary to reduce fentanyl receptor occupancy below 50%

# This work was recently published.

- Higher naloxone dosing in a quantitative systems pharmacology model that predicts naloxone-fentanyl competition at the opioid mu receptor level. PLoS One. 2020 Jun 16;15(6):e0234683. doi: 10.1371/journal.pone.0234683. PMID: 32544184

- Brief Report: Higher Fentanyl Exposures Require Higher Doses of Naloxone for Successful Reversals in a Quantitative Systems Pharmacology Model. J. Addiction Research and Adolescent Behaviour. 5(2); doi: 10.31579/2688-7517/034

# How was modeling used to support the dose application?