QSP modeling predicts higher naloxone doses will safely reverse more opioid overdoses and save lives.

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ABM QSP Summit

November 5, 2020

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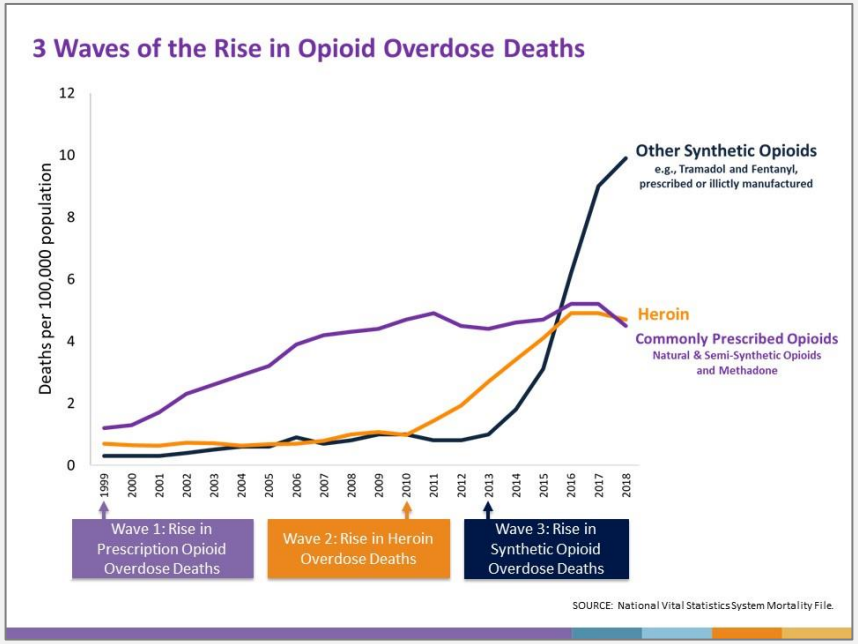
Background

- Epidemiological data from the Centers for Disease Control (CDC) suggests a rise of almost 10% in deaths due to opioid overdoses, which killed approximately 72,000 Americans in 2017, a record number*
- The death toll from opioid overdoses is higher than the peak yearly death totals from HIV, car crashes, or gun deaths
- The CDC has attributed the largest increase in deaths to illicitly manufactured synthetic opioids, such as fentanyl
- Fentanyl is considered 100 times more potent than morphine
- Receptor occupancy by fentanyl and the ability of naloxone to displace this opioid are key factors in reversing opioid toxicity



https://www.cdc.gov/drugoverdose/epidemic/index.html

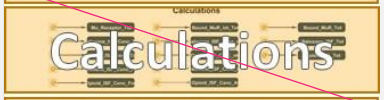
*Moss 2019 PMID: 30777088

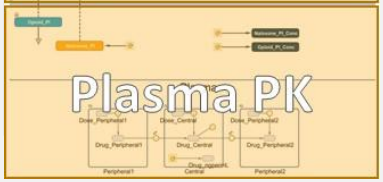
We hypothesize that higher doses of naloxone are needed to combat this trend of overdoses.

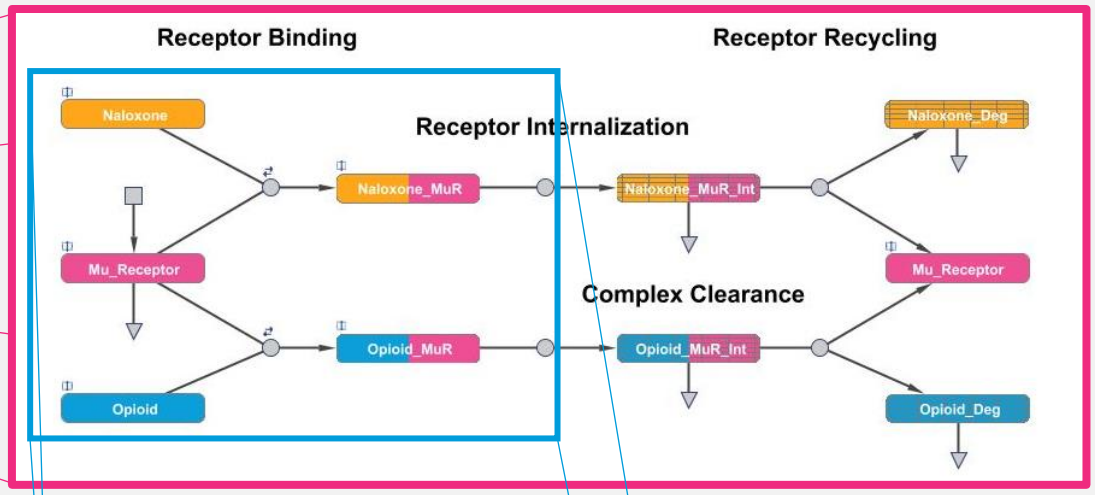
- Associated with the dramatic increase in deaths due to fentanyl overdoses have been resuscitations requiring multiple doses of naloxone at the current approved doses (2 mg intramuscular (IM) or 4 mg intranasal (IN))

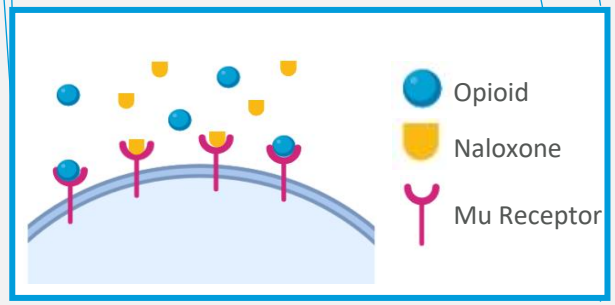
- We developed a mathematical model of the opioid mu receptor occupancy of fentanyl with different doses of naloxone (5 or 10 mg IM) to evaluate the hypothesis that higher doses are beneficial

Fentanyl and Naloxone Compete for Mu Receptor







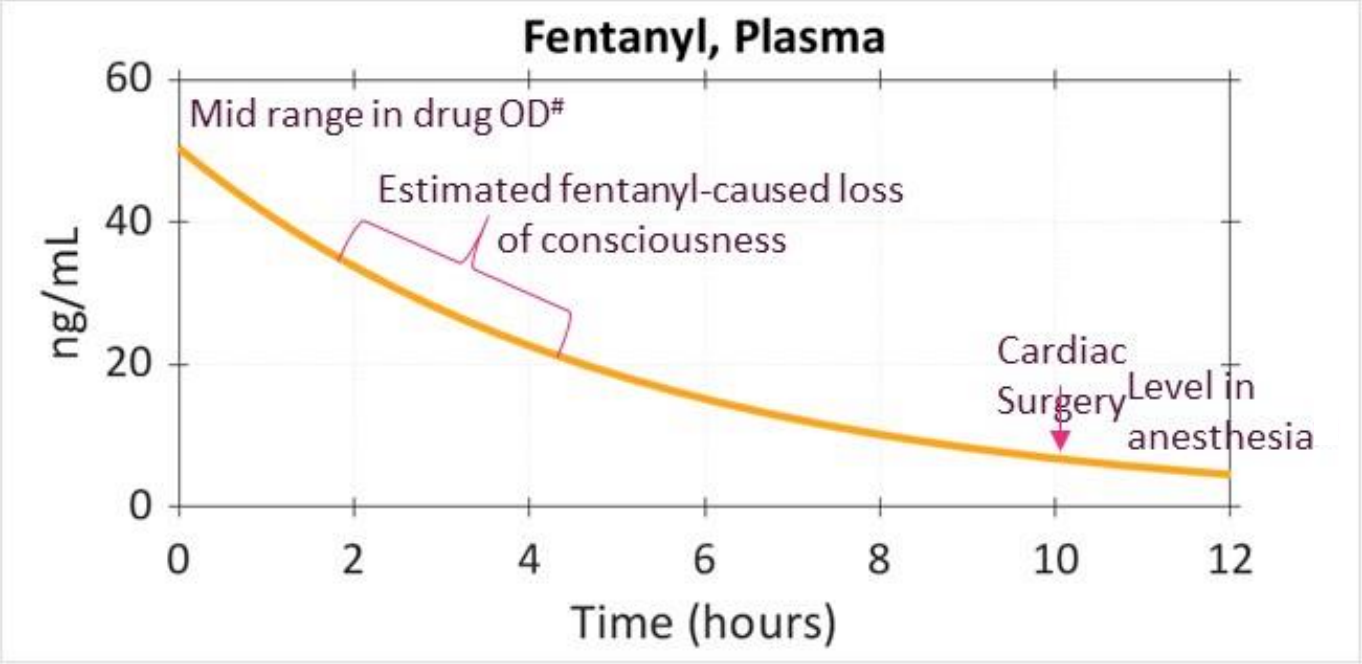


Competitive Receptor Binding Depends on:

- 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

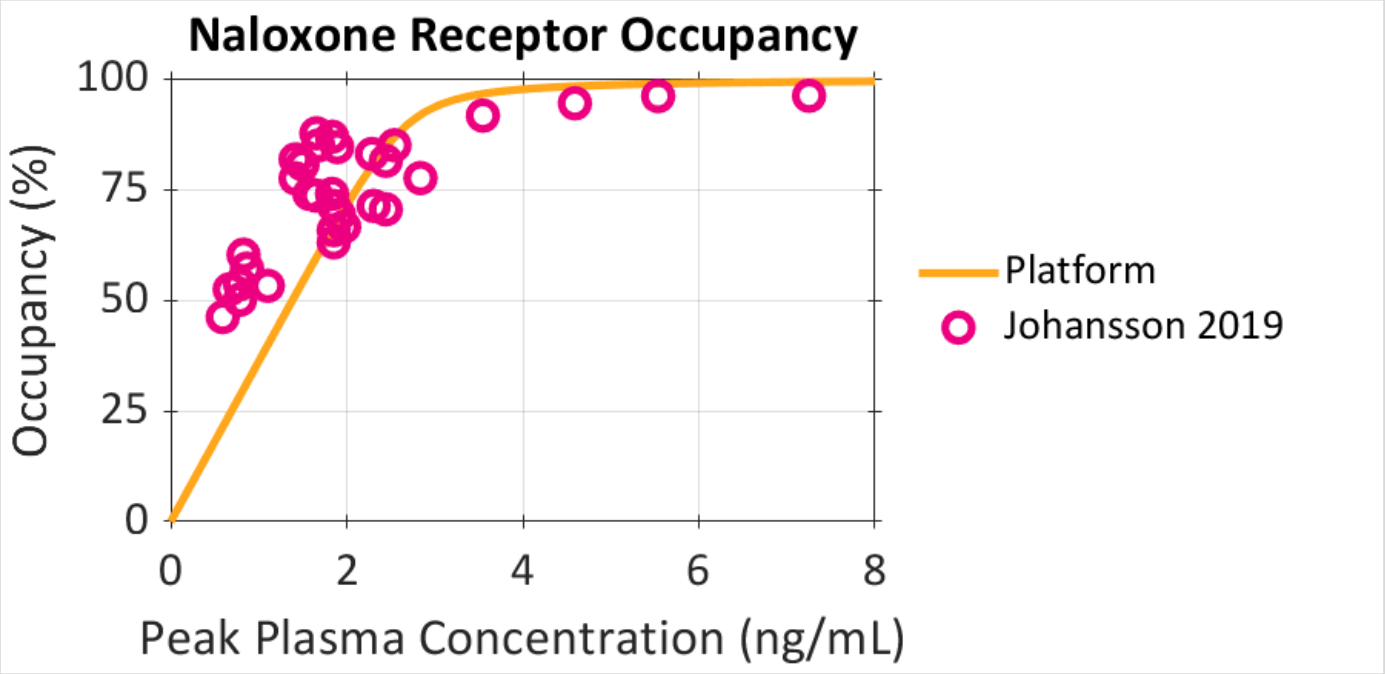
Opioid overdose victoms may have much higher drug levels than occurs in standard clinical use.



- Simulated fentanyl concentrations correspond to an 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 route of administration
- Fentanyl plasma half-life is ~3.5 hours**

*Gill 2013 PMID: 22890811
**Corli 2014 PMID: 24346227

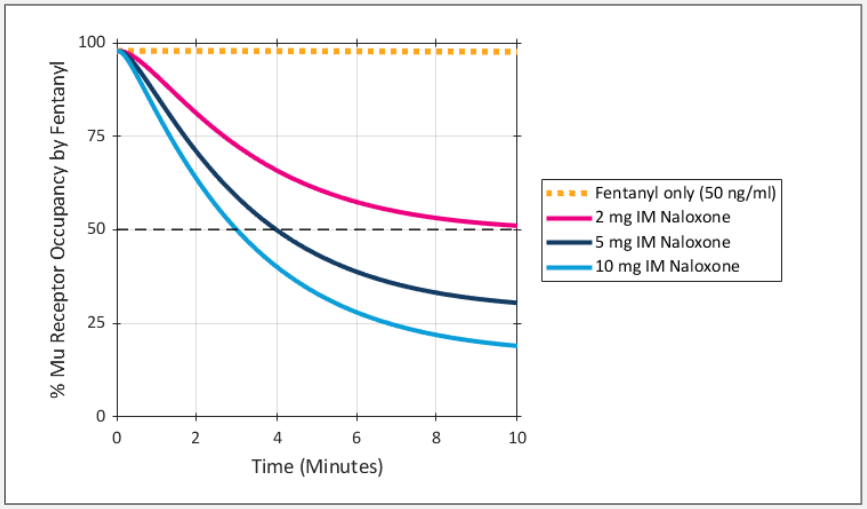
The model incorporated publicly available data for calibration and qualification.

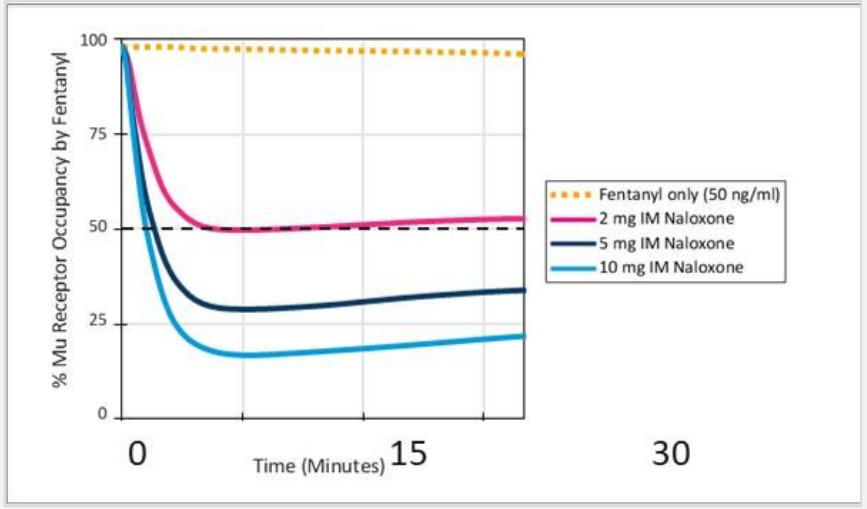


- The figure shows an example comparison of data with model simulation results
- Mu receptor occupancy (RO) by naloxone increases with naloxone dose*
- Dose response and duration of mu receptor occupancy by fentanyl is consistent with reported therapeutic ranges and symptoms (references upon request)

*Johansson 2019 PMID: 30867551

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



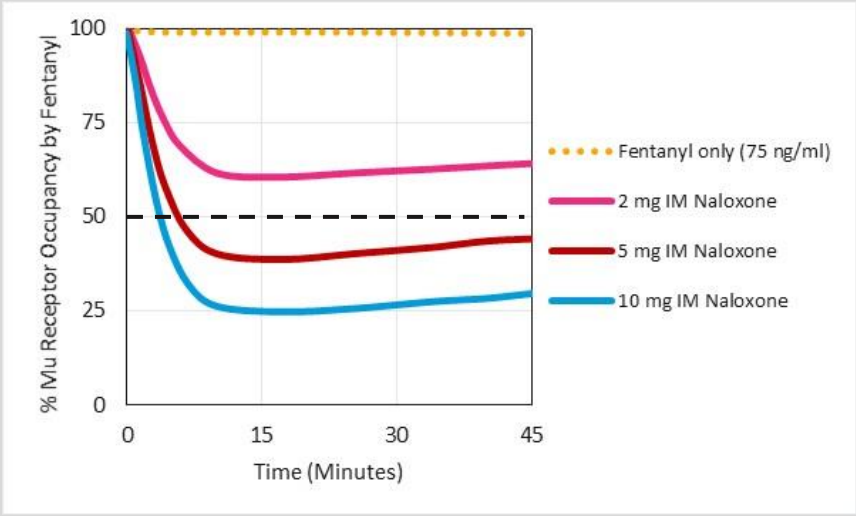


- Fentanyl at 50 ng/ml is a median overdose concentration*
- 50% mu RO (dashed black line) is generally considered the point at which the patient loses the ability to breathe
- Higher doses of naloxone reduce mu RO by fentanyl faster and to a greater extent than the currently approved 2 mg IM dose
- Renarcotization can be seen for the 2 mg dose of naloxone as fentanyl RO increases above 50% over time (right) and is not observed at the higher doses

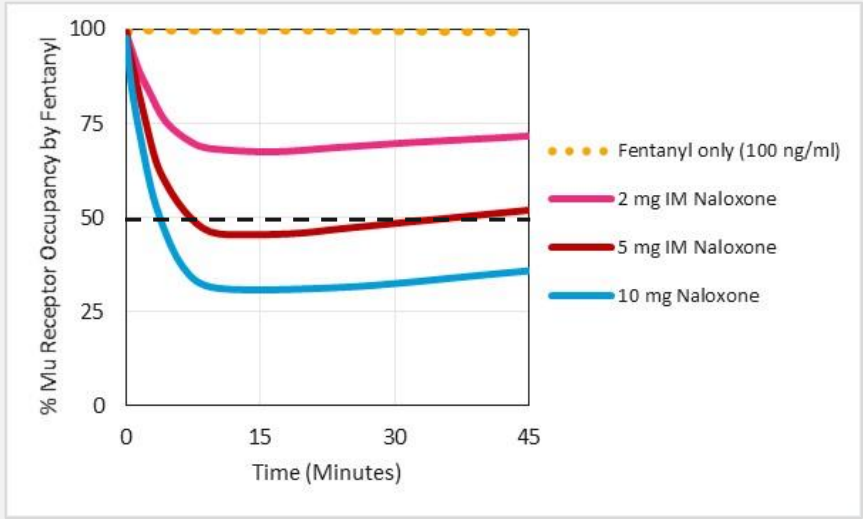
*Gill 2013 PMID: 22890811

At higher levels of fentanyl, higher doses of naloxone are needed to reduce receptor occupancy below 50%.

Fentanyl 75 ng/ml



Fentanyl 100 ng/ml



- In overdose victims, fentanyl concentrations can range between 1 and 102 ng/ml*

*Gill 2013 PMID: 22890811

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:

RESEARCH ARTICLE

Higher naloxone dosing in a quantitative systems pharmacology model that predicts naloxone-fentanyl competition at the opioid mu receptor level

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- PLoS One. 2020 Jun 16;15(6):e0234683
- https://pubmed.ncbi.nlm.nih.gov/32544184/