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

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Introduction

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- Naloxone is used to treat opioid overdose
- Current dosing recommendations may be too low

Objectives:

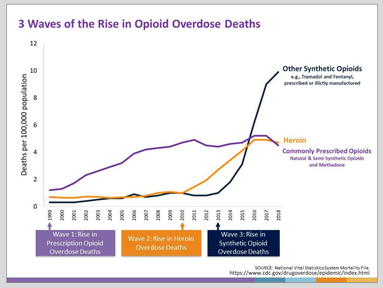
- Develop a quantitative systems pharmacology (QSP) model with relevant opioid, naloxone, and mu-opioid receptor dynamics
- Evaluate naloxone doses in combination with a range of opioid (fentanyl) concentrations
- Assess the benefit of higher doses of naloxone in displacing fentanyl from the receptor

Results

- Higher doses of naloxone reduce opioid receptor occupancy by fentanyl faster and to a greater degree
- Higher doses also reduce the risk of renarcotization

Results

Naloxone blocks opioid binding to its receptor and can prevent death from opioid overdose.



The number of deaths due to **synthetic opioids** has increased dramatically in the last 5 years. Current recommended doses (2 mg) of **naloxone for overdose reversal** may be inadequate, and redosing is often required.

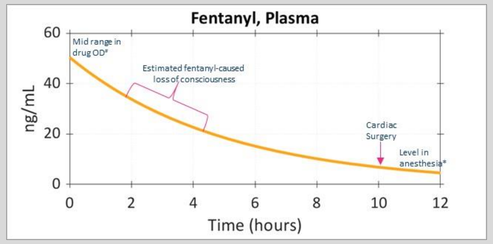
Because the device is used in a community setting, ethical clinical trials are not possible.

Naloxone would be administered with an intramuscular injection device by caregivers or members of the community.

Conclusion

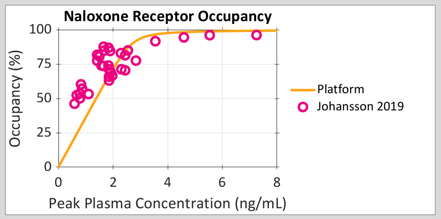
Higher naloxone doses are predicted to safely reverse more opioid overdoses and save lives.

Opioid overdoses may have much higher drug levels than standard clinical use of the drugs.



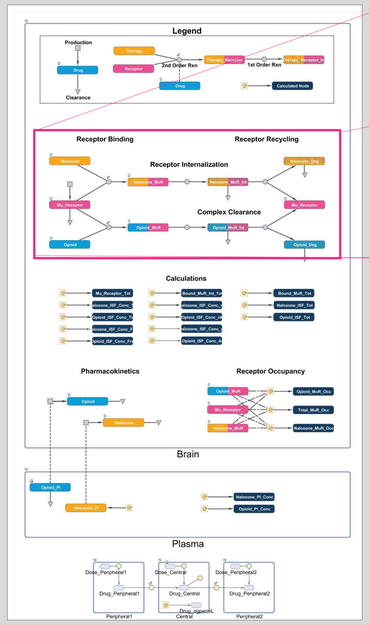
The current standards for naloxone delivery were estimated from clinical use of fentanyl and other opioids. Overdose victims may have developed a tolerance for opioids and take larger doses to compensate.

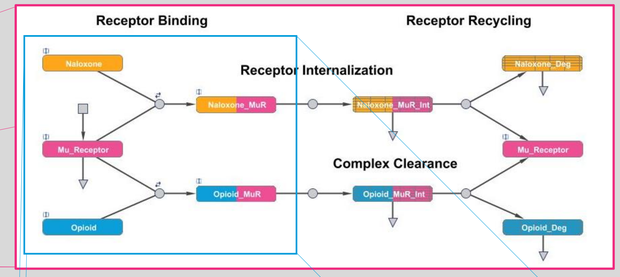
The model incorporated publicly available data for calibration and qualification.

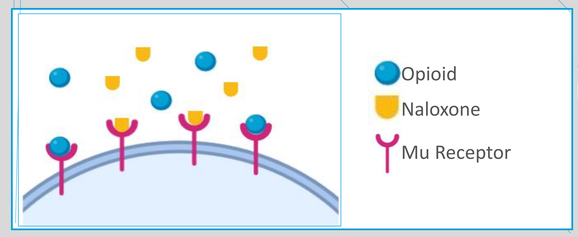


The figure shows an example of data comparison with model simulations. Naloxone receptor occupancy increases as naloxone dose increases, consistent with data from Johansson et al. 2019, Neuropsychopharmacology. 44(9):1667-1673.

The model was developed to support drug approval without a clinical trial.





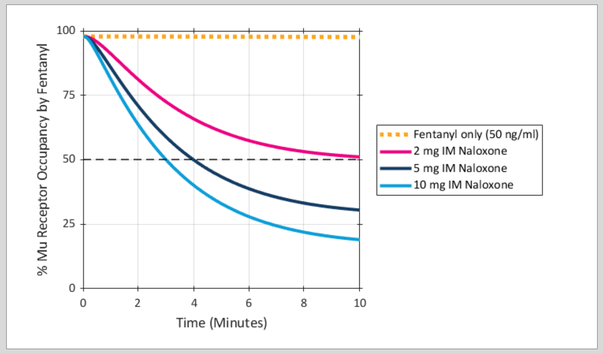


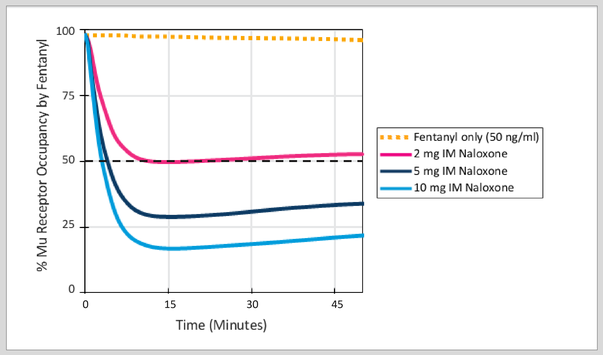
Competitive receptor binding depends on:

- Ligand concentrations
- K_{on}, K_{off}

The QSP model includes relevant opioid, naloxone, and mu-opioid receptor dynamics in the brain and plasma.

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





Fentanyl was given to 50 ng/mL and then naloxone dosed from 0-10 mg IM. 50% Mu receptor occupancy (dashed black line) is thought to be the point where the patient loses the ability to breathe. Higher doses of naloxone reduce mu receptor occupancy by fentanyl faster and to a greater extent than the 2 mg dose. Renarcotization can be seen for the 2 mg dose of naloxone as fentanyl receptor occupancy increases above 50% over time (right).

Read the paper!

SCAN ME

This work was recently published: Moss RB, Pryor MM, Baillie R, Kudrycki K, Friedrich C, Reed M, Carlo DJ. 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. https://pubmed.ncbi.nlm.nih.gov/32544184/.

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