# Higher Fentanyl Exposures Require Higher Doses of Naloxone for Successful Reversals in a Quantitative Systems Pharmacology Model

**Objectives:** Reversal of fentanyl overdose is an urgent unmet medical need, and controlled clinical trials are not practical given the risk. Previously, we reported on an opioid receptor quantitative systems pharmacology (QSP) model to evaluate naloxone to treat fentanyl overdose within a typically observed range[1]. We hypothesized that higher doses of fentanyl would require higher doses of naloxone for successful reversal.

**Methods:** In this study, we extended our model to include higher systemic levels of fentanyl (up to 100 ng/ml) and a newly approved 8 mg intranasal (IN) naloxone dose (equivalent to 4 mg intramuscular (IM)).

**Results:** As expected, at the lower peak fentanyl concentrations (25 ng/ml and 50 ng/ml), the simulations predicted that 2 mg, 4 mg, 5 mg, and 10 mg IM doses of naloxone displaced fentanyl and reached below the 50% receptor occupancy within 10 minutes. However, at the concentration of 75 ng/ml, the simulation predicted that the 2 mg dose of naloxone failed to reach below the 50% occupancy within 10 minutes. Interestingly, at the highest peak concentration of fentanyl studied (100 ng/ml), the model predicted that the 4 mg of naloxone IM (equivalent to 8 mg IN) also failed to reach below the threshold of 50 % occupancy within 10 minutes or even within 15 minutes (data not shown). In contrast, the model predicted successful reversals when 5 and 10 mg IM doses were utilized.

**Conclusions:** These results support the notion that acutely administered higher doses of naloxone are needed for rapid and adequate clinical reversal, particularly when higher systemic exposure of the potent synthetic opioids occurs.

**References:**

[1]PLoS One. 2020 Jun 16;15(6).

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