

Using mouse models to investigate why fentanyl is so deadly

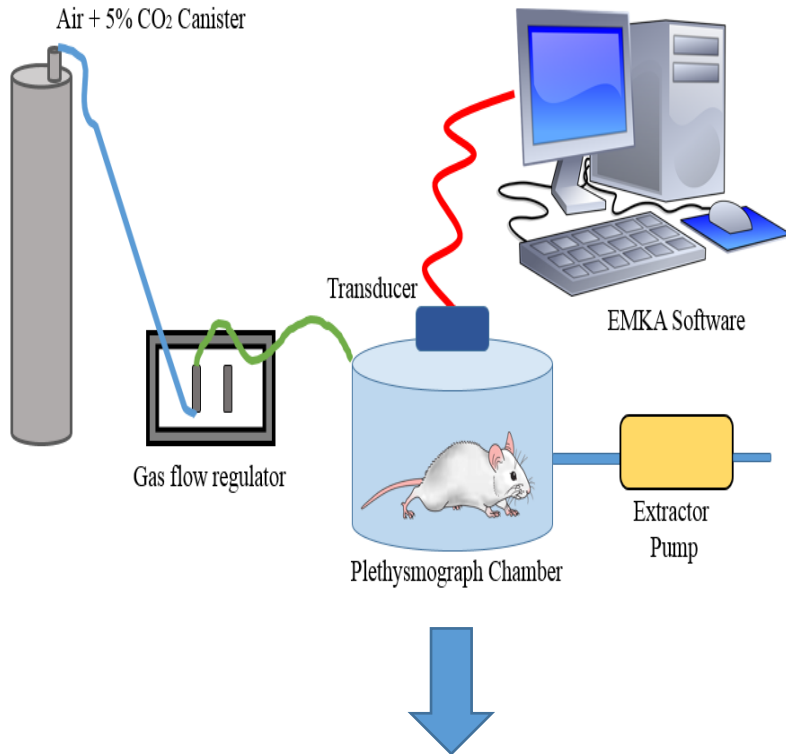
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No conflicts of interest to declare

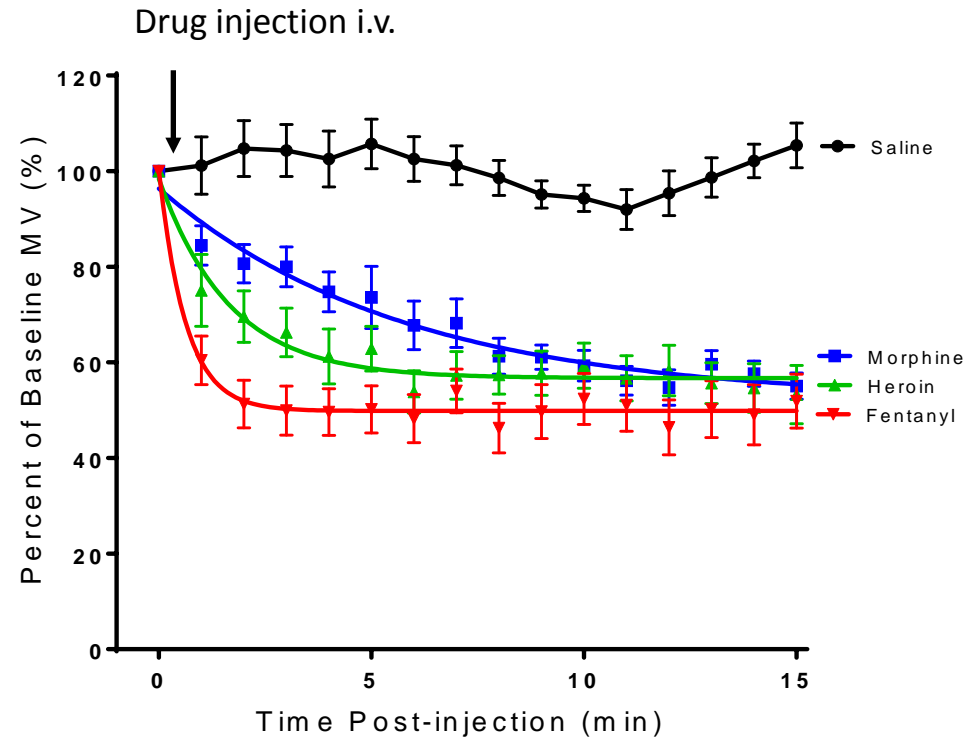
Why are fentanyls so deadly?

- Faster rate of onset of respiratory depression
- Muscle stiffness (wooden chest) making it harder to breathe
- Lower cross tolerance between heroin and fentanyl
- Resistance to naloxone reversal

Fentanyl has a faster rate of onset than heroin and morphine



- Respiratory rate
- Depth of breathing (tidal volume)



Equi-effective doses – same level of respiratory depression

Fentanyl induction of muscle stiffness

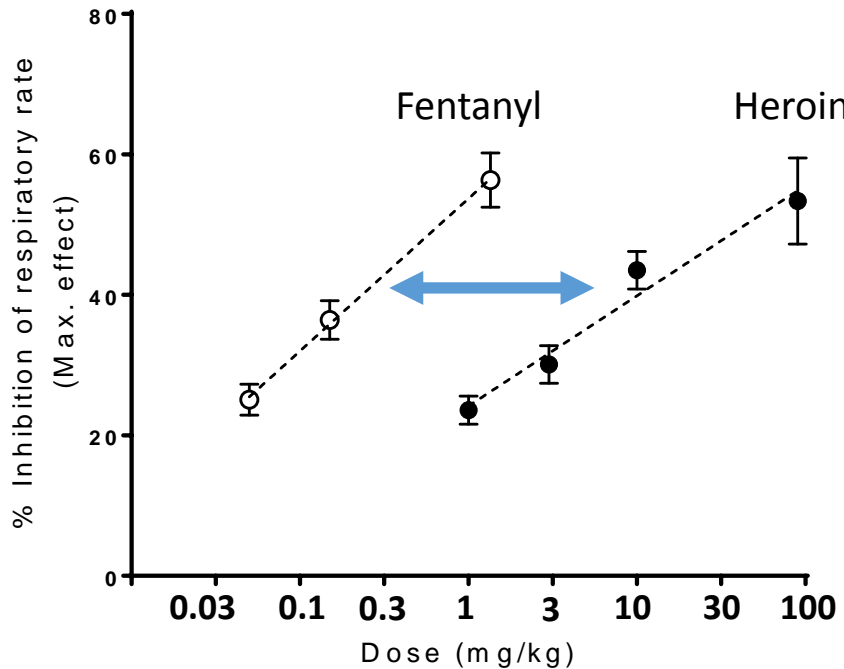
Fentanyls induce skeletal muscle stiffness

- effect on intercostal and diaphragm muscles makes it harder to breathe (referred to as 'wooden chest')

- **Fentanyl depresses respiratory rate and tidal volume**
- **Is the effect on tidal volume due to muscle stiffness?**
 - comparison of potency between fentanyl and heroin

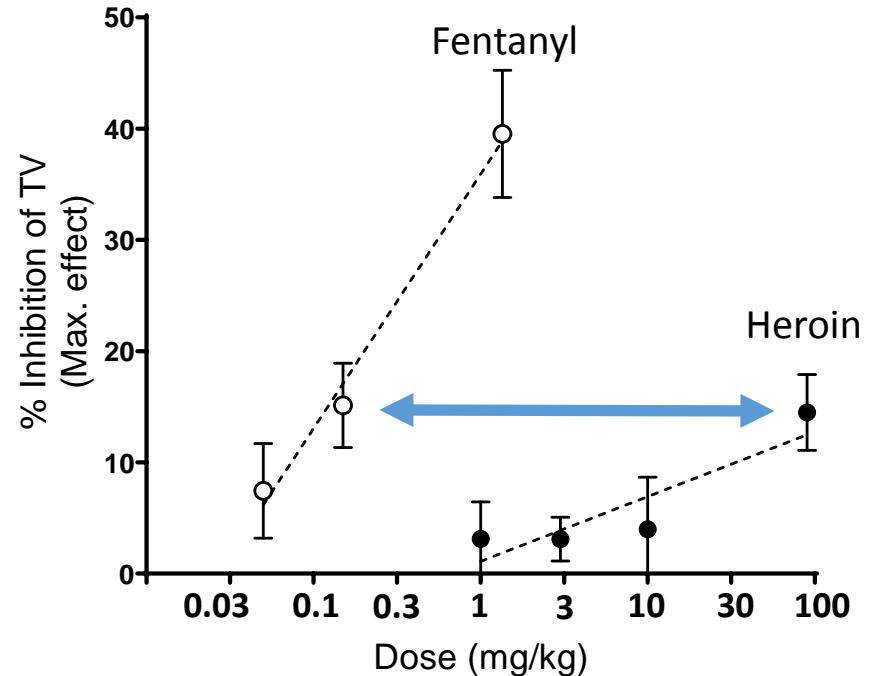
Fentanyl is far more potent than heroin at depressing respiration and tidal volume

Respiratory rate



Fentanyl is 70x more potent than heroin

Tidal Volume



Fentanyl is 600x more potent than heroin

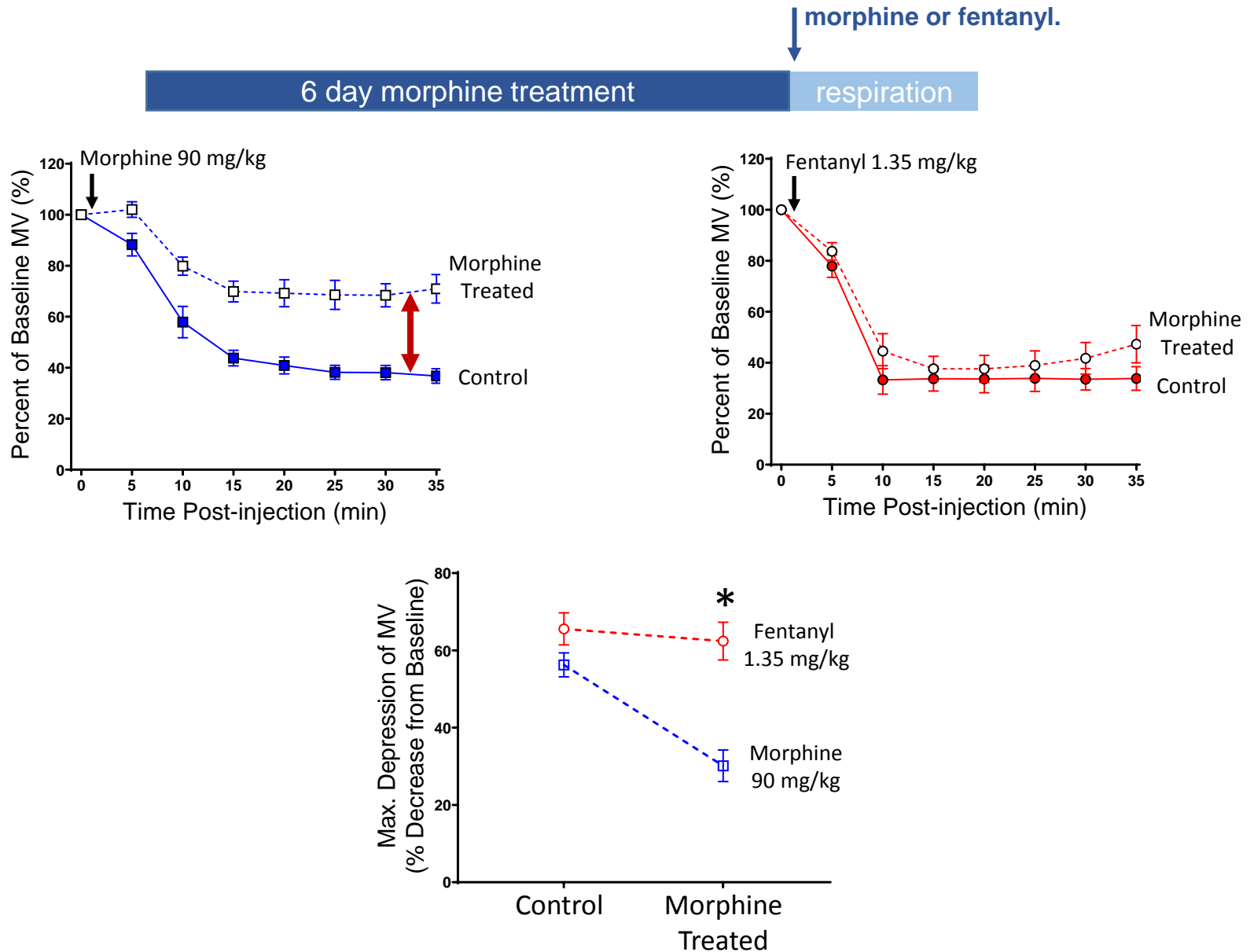
Cross tolerance between fentanyl and morphine

- Few opioid users use fentanyl as their first choice drug.
- Heroin is cut with fentanyl to increase potency.
- Heroin users develop tolerance to respiratory depression.

Question

Does tolerance to morphine produce cross tolerance to fentanyl?

Low cross tolerance between morphine and fentanyl



Is more naloxone required to reverse fentanyl?

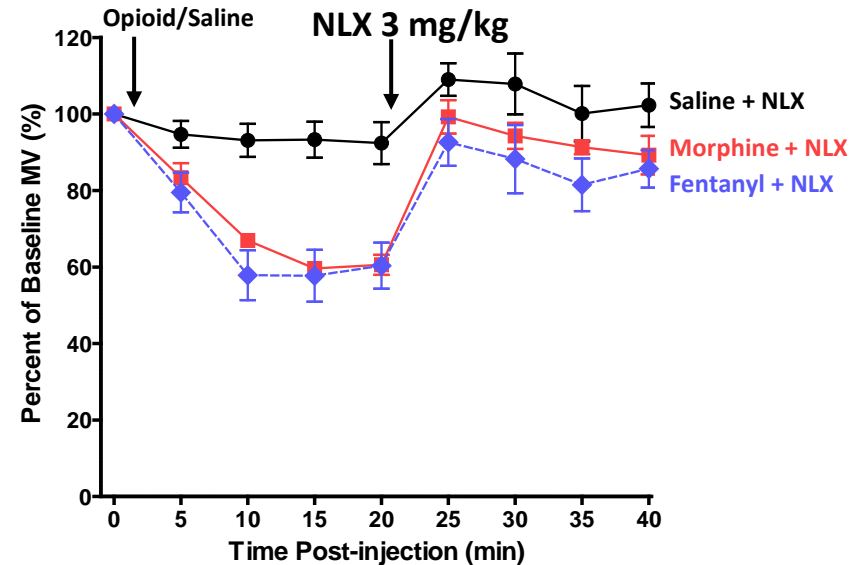
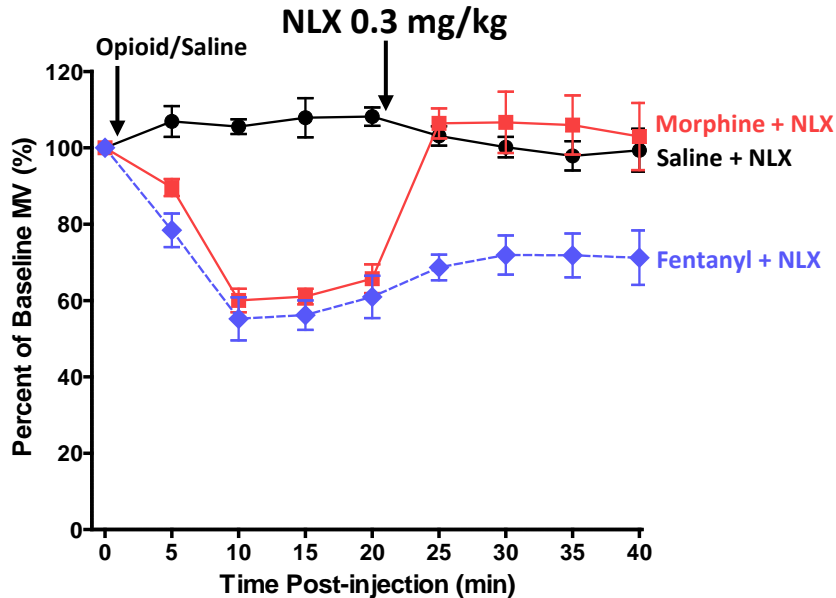
Potential reasons

- because large amounts of fentanyl were taken
- an anomalous pharmacological interaction

To investigate this

- We administered doses of morphine and fentanyl that produced the **SAME** level of respiratory depression
- Examined the ability of naloxone to reverse the respiratory depression

Fentanyl is resistant to reversal by naloxone



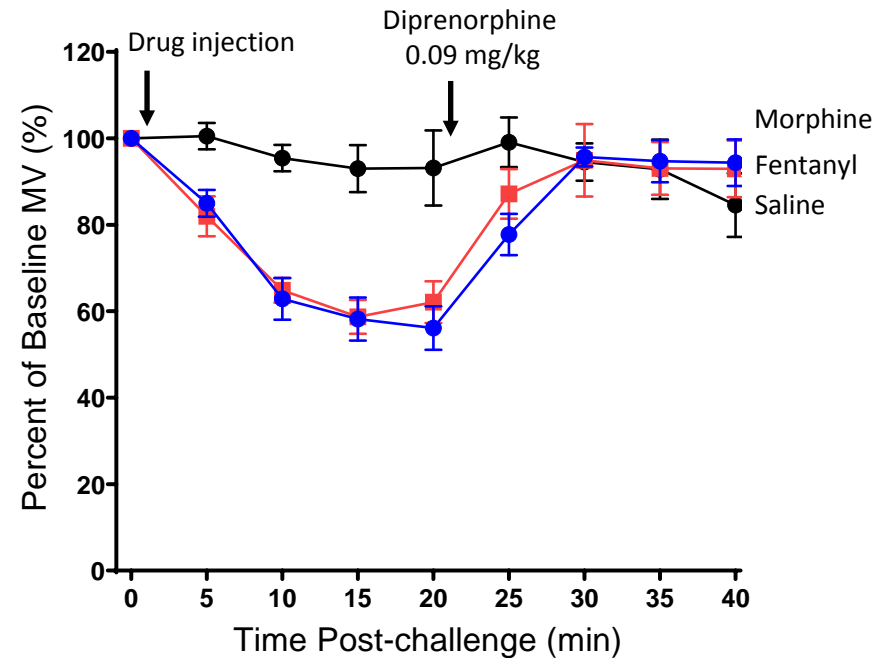
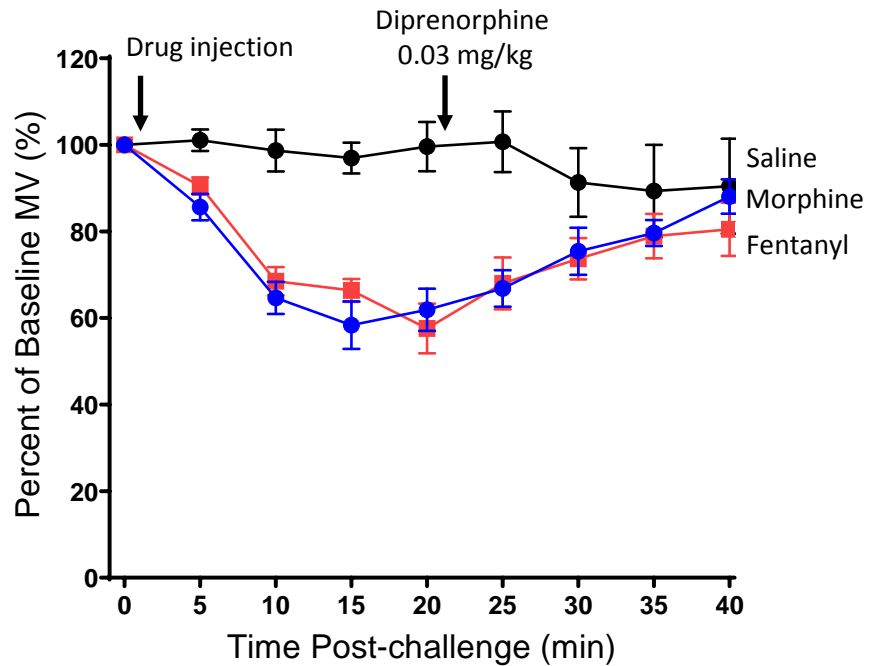
A 10 fold higher dose of naloxone is needed to reverse fentanyl to the same extent as morphine

Are there alternative antagonists to naloxone?

- Fentanyl is highly lipophilic
- A more lipophilic antagonist might be more effective than naloxone to reverse fentanyl

Diprenorphine is a lipophilic opioid antagonist

Diprenorphine reverses fentanyl and morphine respiratory depression equally



Diprenorphine reverses morphine and fentanyl **EQUALLY**

Conclusions

These data suggest fentanyl is more deadly due to:

- Its faster rate of onset of respiratory depression
- Induction of muscle stiffness
- Low cross tolerance to fentanyl for users of heroin
- Resistance to reversal by naloxone