

# Naloxone as a Mu-Receptor Antagonist: A Patient Case of Opioid Induced Respiratory Depression

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## Abstract

Opioid overdose is a major cause of respiratory depression, characterized by shallow or slow breathing. If not treated, it can be potentially life threatening. Naloxone, an opioid antagonist is one of very few drugs used to reverse opioid overdose and improve respiration.

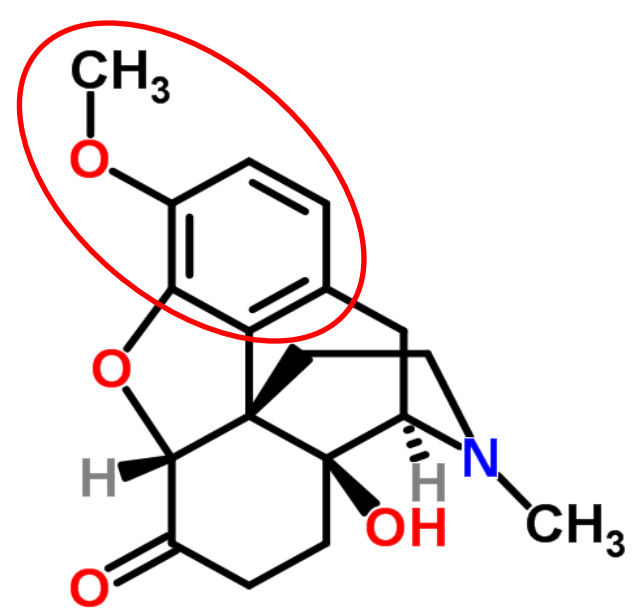
## Introduction

RC, a patient in good overall health, was admitted to the hospital for a total hip replacement. After a successful surgery, the patient was given oxycodone and hydromorphone to control postoperative pain. The combination of these two opioid medications led to respiratory depression. He was successfully treated using IV naloxone and supplemental oxygen.

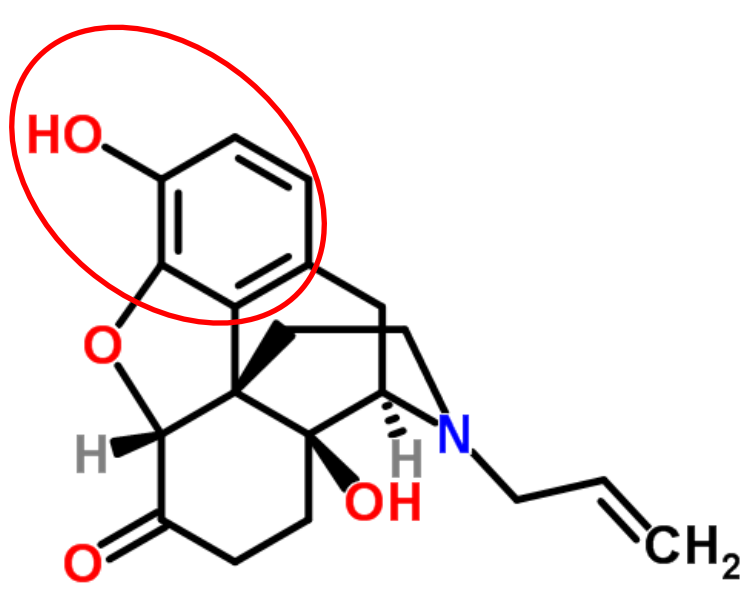
Opioids are mu opioid receptor (MOR) agonists clinically used for pain relief. There are two MORs;  $\mu_1$  is responsible for the desired analgesic effects by blocking pain signal transmission from neuron to neuron, and  $\mu_2$  is responsible for undesired effects including respiratory depression (1).

Opioid analgesics, like the oxycodone and hydromorphone given to RC after surgery, are not selective for one type of MOR so both effects are seen with their use (2). As more drug binds the MOR, the analgesic and respiratory depressive effects become enhanced. In an overdose, respiratory depression overpowers the analgesia, causing a life-threatening situation. This can be reversed with a MOR antagonist like naloxone, which has competitive reversal effects against opioid agonists.

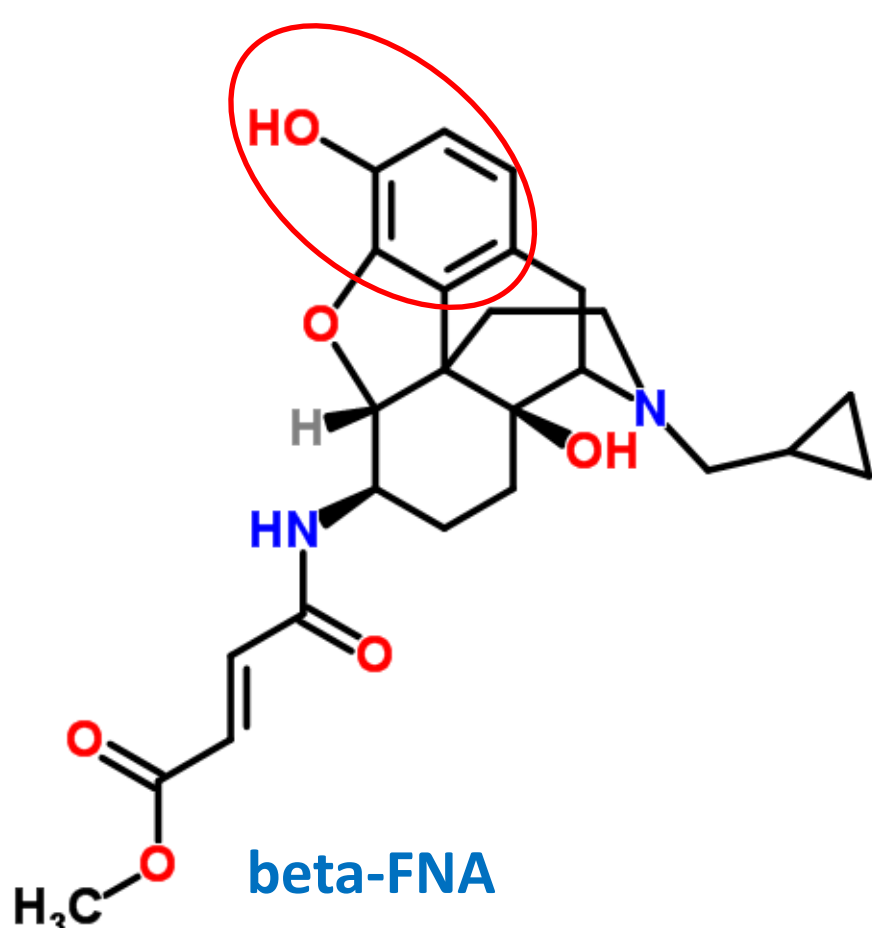
The structural similarity between naloxone and oxycodone shows how small changes in a pharmacophore, shown circled in red, have significant changes in the action of drugs (see Figure 1). The benefit and mechanism of MOR antagonists continues to be an area of focus in research. Recently the crystal structure of beta-funaltrexamine (beta-FNA), a morphinan antagonist bound to the mouse MOR, was isolated and analyzed. There is 94% sequence identity between the mouse and human MOR, which suggests both proteins share a similar structure (3). This similarity provides a new avenue for researchers to explore, to optimize the use of and to design new MOR agents. This new crystal structure of beta-FNA will be the focus of our molecular story.



oxycodone



naloxone



beta-FNA

Figure 1: Chemical structure of mu agonist (oxycodone) and mu antagonists (naloxone and beta-FNA) Created using [www.chemspider.com](http://www.chemspider.com)

The CREST Program is funded by grant #1022793 from NSF-CCLI.

## Molecular Story

Seen in Figure 1, oxycodone, naloxone and beta-FNA all share similar structural characteristics that allow them to bind to the MOR. Oxycodone has a tyrosine structural motif, which includes a benzene ring with a methoxy substituent. Naloxone and beta-FNA have a tyrosine mimic including a benzene ring with a hydroxyl substituent. Additionally, the cyclopropyl group gives beta-FNA its antagonist action (4).

Figure 2 shows beta-FNA binding with amino acids of the MOR (Asp 147, Tyr 148, His 297 and Lys 233).

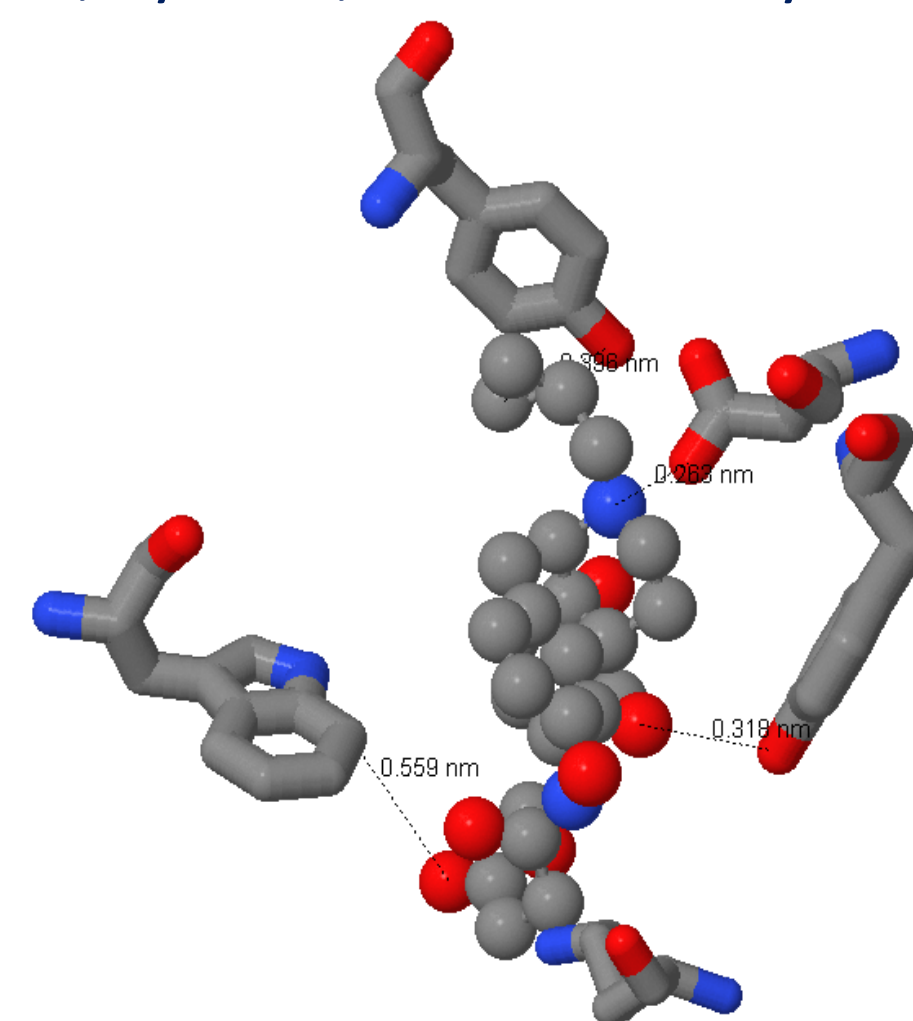


Figure 2: Beta-FNA (PDB Code 4DKL) bound to amino acids. Carbon (gray), Oxygen (red), Nitrogen (blue), numbers represent distances between atoms (in nanometers)

- Tyr 147 forms an ionic bond between the drug and the MOR
- Tyr148 forms a hydrogen bond between the oxygen in the five member ring and the receptor
- His297 uses two free water molecules to hydrogen bond with the ligand.

The ribbon structures (Figure 3 and Figure 4) show beta-FNA bound in the MOR binding pocket.

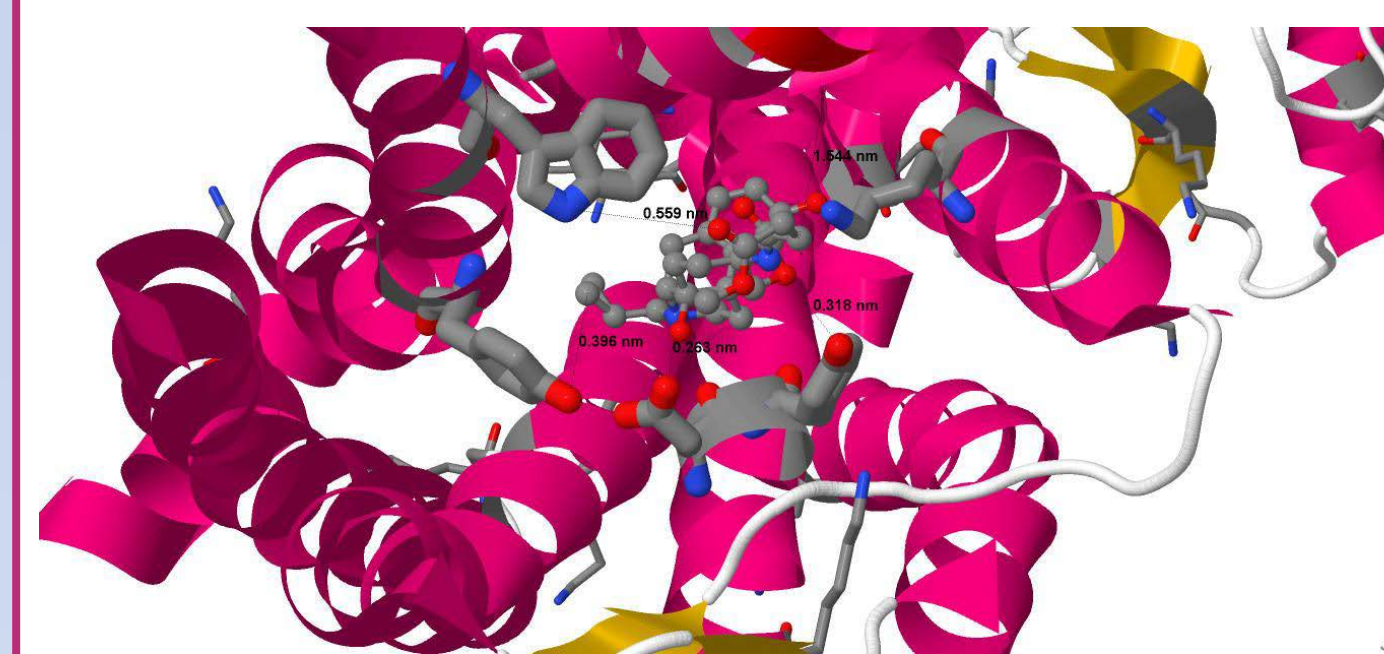


Figure 3: Top view of Beta-FNA (PDB Code 4DKL) bound in the MOR. Backbone (pink), Carbon (gray), Oxygen (red), Nitrogen (blue), numbers represent distances between atoms (in nanometers)

Instead of naloxone bound, beta-FNA is shown due to the fact that it irreversibly binds the MOR, which aids in crystallization and visualization of the drug to MOR binding.

It is important to note that natural ligand binding occurs by ionic interactions in the MOR. The covalent bond of beta-FNA between the 6' carbon substituent and Lys233 was done purposefully to stabilize the interaction for better visualization (5).

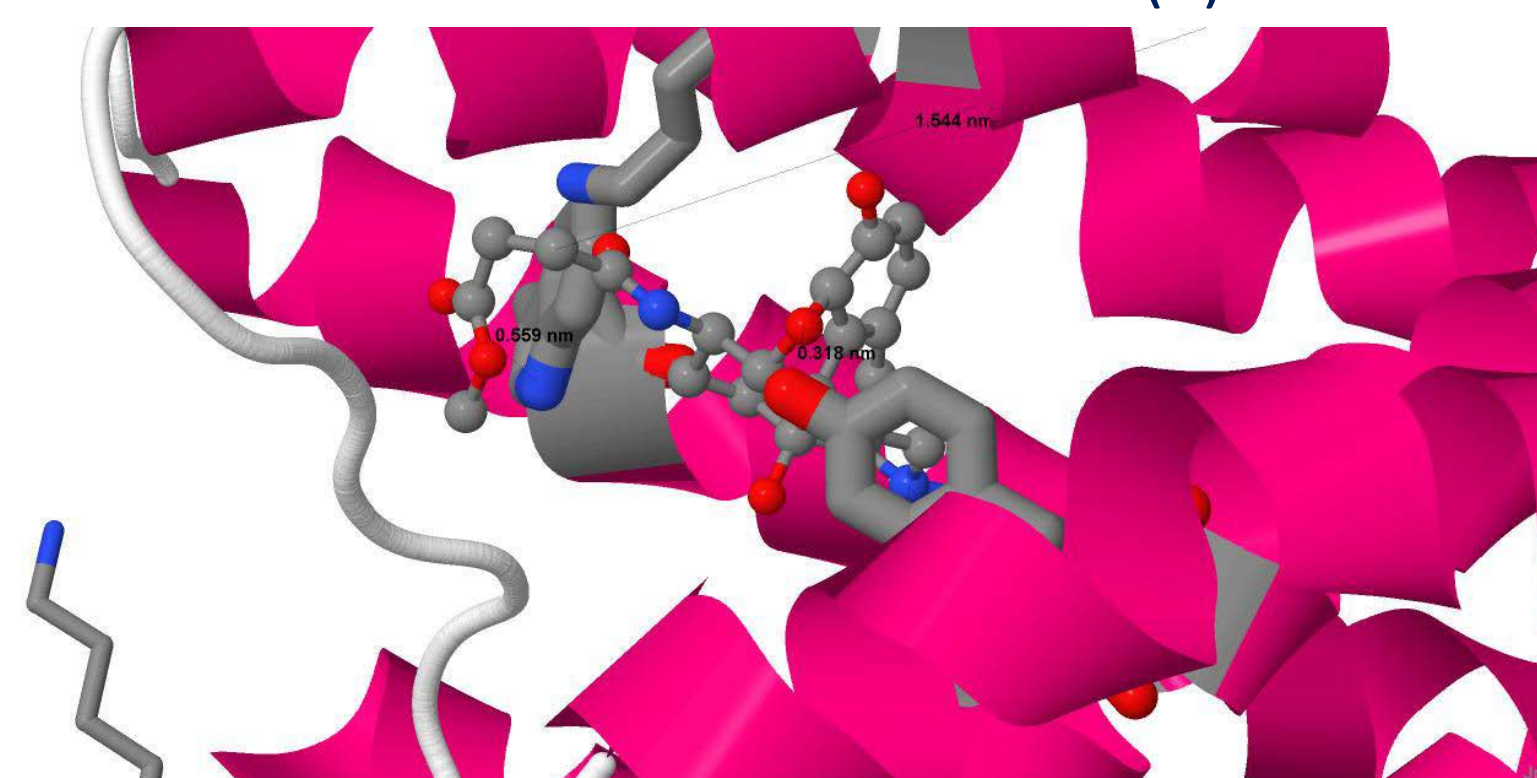


Figure 4: Rotated image of Beta-FNA (PDB Code 4DKL) to visualize the MOR binding pocket. Backbone (pink), Carbon (gray), Oxygen (red), Nitrogen (blue), numbers represent distances between atoms (in nanometers)

Visualization of antagonist binding can help us better understand how drugs like naloxone work to prevent further binding of opioid to the receptor and reverse undesirable effects. Specifically, the hydroxyl substituent on the benzene ring of naloxone gives it a higher affinity for the MOR, which leads to preferential binding of naloxone and displacement of oxycodone from the receptor, reversing respiratory depression (6).

One downfall of naloxone is a very short half-life compared to oxycodone. To ensure that the patient does not fall back into respiratory depression, a naloxone continuous infusion is required so that the antagonistic effect can outlast the agonist (6).

## Future Work

Despite naloxone's rapid action as an opioid antagonist, it still has a short half-life compared to that of oxycodone.

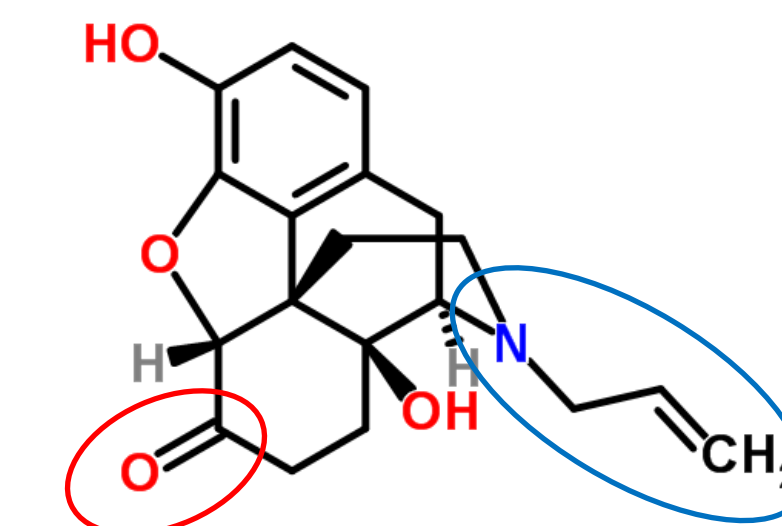


Figure 5: Naloxone structure with possible areas of modification highlighted

Naloxone is metabolized in the liver primarily by glucuronide conjugation with naloxone-3-glucuronide as the major metabolite. Further research to improve half-life should include areas such as modification of the nitrogen substituent to prevent N-demethylation, circled in blue in Figure 5, and the 6-ketone to slow glucuronidation, circled in red in Figure 5.

Another option would be to focus on the agonist side and modify our current opioids to eliminate or decrease adverse effects, such as respiratory depression. To minimize the negative effects of the opiate pain medications, the difference in receptor structure between  $\mu_1$  and  $\mu_2$  needs to be the deciding factor when designing a receptor selective opiate pain medication.

When making modifications to either the agonist or antagonist, it is important to maintain the 3-OCH<sub>3</sub> or 3-OH structure, which allows these drugs to bind to the MOR and produce their effects of pain relief or opioid reversal, respectively.

## Summary

Naloxone binds to the MOR as an antagonist to reverse opioid overdose and respiratory depression. This drug is extremely important, especially in emergency situations when patients cannot breathe on their own. Modifications to increase naloxone's half life to match that of oxycodone would eliminate the need for continuous infusions and improve the efficacy of the drug. Alternatively, improved specificity of current opioid medications would help to eliminate the adverse effects of  $\mu_2$  receptor binding.

## References

- Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. *Pain Physician*. 2008;11(2 Suppl):S133–153.
- Inturrisi CE. Clinical pharmacology of opioids for pain. *Clin J Pain*. 2002;18(4 Suppl):S3–13.
- Jose Manuel Perez-Aguilar, Jeffery G. Saven, Renyu Liu. Human  $\mu$  Opioid Receptor Models with Evaluation of the Accuracy Using the Crystal Structure of the Murine  $\mu$  Opioid Receptor. *J Anesth Clin Res*. 2012;3(6):1–5.
- David A. Williams, William O. Foye, Thomas L. Lemke. *Foye's Principle of Medicinal Chemistry*. 5th ed. Lippincott Williams & Wilkins; 2002.
- Manglik A, Kruse AC, Kobilka TS, Thian FS, Mathiesen JM, Sunahara RK, Pardo L, Weis WI, Kobilka BK, Granier S. Crystal structure of the  $\mu$ -opioid receptor bound to a morphinan antagonist. *Nature* 2012 May;485(7398):321–326.
- Yassen A, Olofsen E, Van Dorp E, Sarton E, Teppema L, Danhof M, Dahan A. Mechanism-based pharmacokinetic-pharmacodynamic modelling of the reversal of buprenorphine-induced respiratory depression by naloxone: a study in healthy volunteers. *Clin Pharmacokinet* 2007;46(11):965–980.