

Naloxone: An Opioid Antagonist

Dr. Joseph E. Graas, Scientific Director
Dr. Renee Kilmer, Medical Director
Dr. Edward Moore, Medical Director
Dr. Karen Wagersmith, Scientific Director

An opioid agonist is a drug that activates opioid receptors in the brain. An opioid antagonist is a drug that blocks opioids by attaching to the opioid receptors without activating them. Agonist and antagonist are chemicals that have actions at the binding site of receptors on neurons or other cell types. When a chemical or drug acts as an agonist it elicits a neural response if it comes into contact with a receptor and outcompetes any other molecule. Antagonist do not have a reciprocal function in the sense of the reverse activity of the agonist. Rather, in sufficient quantities, a true antagonist will displace the agonist without eliciting a neural response. Thus, opioid antagonists cause no opioid effect themselves and block full agonist opioids. Receptors for the opioids are the MOR, DOR and KOR, after the Greek symbols mu, delta, and kappa together with O for "opioid" and R for "receptor". These acronyms are functional notations for the different activity that each receptor has in the body.

Naloxone is a full antagonist and will block the activity of the opioid compound at the receptor. It is widely used by emergency medical personnel and first responders when an opioid overdose is determined. Naloxone must be administered within a very small time window to save a person's life. Opioids above a certain level in a person's system will immediately inhibit the breathing process. In the opioid family of drugs, the fentanyl analogues are the most powerful (as determined by the dose) that will completely inhibit the respiratory system. With the opioid crisis and the adulteration of heroin and other opioids with fentanyl, the overdose consequences are serious. Further the availability of cheap fentanyl has led to the rise in deaths from these drugs. Publication of a study

from The Center for Disease Control on the deaths caused by opioids during the years from approximately 1999 to 2017 yields the following numbers:

- Deaths involving any opioid rose from 8,048 to 47,600.
- Deaths due to heroin rose from 2,000 to 15,958.
- Deaths caused by the synthetic opioids, which was primarily fentanyl, rose from approximately 500 to 30,000 from 2002 to 2016.

The above number of deaths are per year per 100,000 population in the United States. The numbers increased more rapidly after the year 2014 with an increasing rate change per year.

Naloxone was patented and released in the early 1960's and the Food and Drug Administration (FDA) gave approval for treating opiate overdoses by intravenous or intramuscular injection. This method of introduction of naloxone into the human system in cases of opiate overdose proved cumbersome and impractical. Several alternative delivery systems were effective but were never made available commercially. In 2012 researchers from the National Institute on Drug Abuse (NIDA) and Opiant Pharmaceuticals developed a nasal spray for the rapid introduction of the drug. This provided for a known quantity of the drug to be rapidly applied to the nasal cavity. This device was approved by the FDA in November 2015, which led to the commercial distribution of Narcan nasal spray in the United States. The FDA changed the regulatory category for Narcan in June of 2018 to make it readily available "over the counter". This change was in direct response to the need for this medication for rapid availability in an overdose situation. Auto-injectors and other devices for rapid response are becoming available, which are all centered around quick delivery of naloxone by

someone in direct proximity to a person in an opioid overdose crisis.

Several oral medications are available in medical and pain management practices that contain opioids, but also contain naloxone. The formulation contains the specific opiate along with a measured amount of naloxone to deter misuse by injection. Because naloxone has little effect when taken by mouth, only if the product is dissolved and injected does naloxone act as an antagonist and block opiate action. If injected, naloxone will also block other opioid drugs taken in addition to the prescribed drug. Examples of these drugs are as follows:

- Talwin - pentazocine with naloxone for pain management treatment.
- Suboxone Zubsolv - buprenorphine with naloxone for addiction treatment.
- Targiniq ER - a new painkiller that combines oxycodone and naloxone.

Although these drug formulations deter misuse by injection, they can still be addictive even if appropriately prescribed.

In summary, the opioid crisis in the United states is of epidemic proportions, which has resulted in many deaths due to overdose. Illicit drugs are often tainted with varying amounts of fentanyl, making the drug seeker vulnerable to an overdose, no matter what the dose of heroin is. Even a small amount of fentanyl in a normal dose of heroin can be lethal. The availability of the medication naloxone on an over the counter basis is a very important step toward slowing the death rate. The issue with opioids will have to be tackled on many fronts; addiction treatment, reduction of pain medication prescriptions, education, and naloxone availability for emergency use on an individual basis.

References:

Drug Overdose Deaths in the United States, 1999–2016, *Center for Disease Control (CDC)*, Retrieved: 23, December 2017