Naloxone and Naltrexone Look and Sound the Same, But Are Used Differently. Here's Why.

By Josh Bloom — July 17, 2018

NALOXONE

Naloxone (Narcan) is the drug that is given by injection to reverse overdoses, traditionally from heroin (1). It works because it has a much greater affinity for the opioid receptors in the brain than heroin or morphine. Opioids are opioid receptor agonists; it binds to the receptor on the outside of the cell and elicits a pharmacological response on the inside. By contrast, naloxone is an opioid antagonist; it binds to the receptor but does not trigger a pharmacological response (Figure 1).
Figure 1. Agonists vs. antagonists. (A) An unoccupied receptor embedded in a cellular membrane. (B) A receptor bound to its natural agonist, which then sends a signal to the inside of the cell, triggering a series of events leading to a pharmacological response. (C) An antagonist bound to the receptor does not send a signal into the cell and also blocks the agonist from binding. Original figure: Study.com [4]

NALTREXONE

The pharmacology of naltrexone is more complex than that of naloxone (2). Naloxone acts within minutes and lasts for about an hour because of rapid metabolism. This makes it ideal for opioid overdose rescues. Naltrexone acts slowly and lasts longer. Additionally, while the metabolite of naloxone is not an opioid receptor agonist, the metabolite of naltrexone, which is called 6?-naltrexol is also an active agonist. So, the effects of naltrexone arise from both the parent drug and its major metabolite and last about a day.

The difference half-life explains why the two drugs have different purposes. Naltrexone is used to block cravings for both opioids and alcohol but naloxone is not, while naloxone can treat overdoses but naltrexone cannot. Both drugs block the analgesic action of both exogenous opioids and the pleasure response of endogenous endorphins but naloxone acts quickly enough to treat an overdose while naltrexone does not. For these same reasons naltrexone cannot be used to rescue someone from an overdose but can be used to help people who are addicted to opioids have less craving for them.

HOW SIMILAR ARE THEY CHEMICALLY?

The answer here is very similar and for two different reasons. First, it is clear that there is only a very small difference between the chemical structures of the drugs (Figure 2).
Figure 2. The chemical structures of naloxone (left) and naltrexone (right) differ only by the small group (red circle) attached to nitrogen. In naloxone, this group contains an ethylene fragment, while in naltrexone, a cyclopropyl (three-membered ring) fragment replaces ethylene (carbon-carbon double bond).

But the two are even closer than that. It turns out that in the world of drug discovery that sometimes an carbon-carbon bond is a liability in a potential drug. Figure 3 shows two nearly identical (3) inhibitors of hepatitis C. The structure on the left is not a viable molecule because the double bond is probably going to be chemically reactive; chemically reactive drugs are almost always toxic. Chemists at BristolMeyers-Squibb [6] overcame this potential toxicity by replacing the double bond with a cyclopropyl group, which resulted in a stable potent inhibitor of one of the key enzymes required for hepatitis C replication.

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So, two different drugs that are used to combat opioid abuse are used for different purposes, even though on the surface they seem to be indistinguishable. But when the sciences organic chemistry...
and metabolism are applied it all makes sense.

NOTES:

(1) Naloxone is less effective in saving people who have overdosed on fentanyl because fentanyl binds more tightly than heroin to opioid receptors in the brain, so it is more difficult for naloxone to displace it. Multiple doses are frequently needed prompting researchers to look for alternatives to naloxone.

“Naloxone seemed to be great for the older opioids, but now that we’re encountering these nonmedical, ungodly [opioids] like carfentanil… we need to get with the times.”

Dr. Jay Kuchera, Florida Resolute Pain Solutions, TheFix.com [7], July 2018

(2) There are three subtypes of opioid receptors that impact pain called delta, kappa, and mu. There are differences in the binding site and physiological response. This is well beyond the scope of this article.

(3) It is no accident that cyclopropyl and ethylene groups can sometimes be used interchangeably. Because of size and bonding angle, they are very close in chemical properties [8].

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