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# The Use of Agonists and Antagonists in the Treatment of Opiate Addictions

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The Use of Agonists and Antagonists in the Treatment of Opiate Addictions

FYS100 HC: Gotta Have It: Exploring the Science of Addiction

Dr. Thomas E. Hagan

November 16, 2015

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## Abstract

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There are dozens of different opioids available, and each one has a unique structure that allows it to produce specific responses in the body. Some of these drugs even produce responses that can help treat recovering addicts. Since each opioid behaves a little differently, many different options are available for opiate addiction treatment.

Agonists can stop withdrawal symptoms without producing the euphoric highs. At the same time, agonists work to stabilize the body's functions and return them to their pre-addiction levels. Methadone is a common agonist treatment that can decrease an addict's tolerance to heroin or other opiates. Antagonists can block the effects if any further opiates are injected. Naltrexone is used to condition addicts, so they stop associating heroin with highs.

While the various opioid structures provide a wide array of treatment options, it also means that each treatment has its own disadvantages. Therefore, it is supposed that the most effective addiction treatments combine the effects of agonists and antagonists. Buprenorphine is an agonist and a partial antagonist. It combines the two treatment methods to provide a more comprehensive recovery process by conserving important cognitive functioning.

## Introduction

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Heroin is one of the most common addictive drugs. It is estimated that there are 810,000 heroin addicts in the United States each year, according to the National Institute of Health. However, only 20% of these addicts will receive the help that they need, and addicts who do enter treatment are not always guaranteed to remain heroin-free (NIH, 2013). The problem lies in the way that heroin addiction is treated. There are many different drugs available for treatment, and each one varies in its structure, properties, and effects. How do these drugs differ? Which one has the most success? Scientists continue to only grasp for a treatment to an addiction that has been haunting humanity for centuries.

Heroin addiction started in ancient times, with an addictive painkiller called opium (Adams, 2014). Opium is extracted from poppy plants; drugs are then created by extracting the alkaloids in the opium. Morphine and codeine are both synthesized in this way (Adams, 2014).

As people continued to discover the power of opium, they also began to realize its addictive properties (Adams, 2014). This initiated the pursuit to synthesize painkillers that were not addictive. Drugs like oxycodone and heroin are synthesized by altering the chemical structure of morphine, and while these drugs still possess analgesic properties, they are often found to be more addictive. (Adams, 2014).

Molecules like heroin, morphine, codeine, and oxycodone enter the body through ingestion, injection, or absorption, but the body is also able to produce its own natural painkillers. These proteins, named opioids after the exogenous painkillers derived from opium, are coded for by genes in the body. The peptides work to block pain neurons the periaqueductal gray region in the brain, which lessens the body's pain response (Pasternak, 2014). The umbrella term for these endogenous opioid peptides is endorphins. Endorphins can then be broken down into three classes: endomorphins, dynorphins, and enkephalins (Pasternak, 2014).

Each type of endogenous endorphin and exogenous opiate interacts in the body by binding to a specific receptor. In this case, opioid receptors are responsible for the strong effects that these molecules produce in the body (Cong et al., 2015). These highly specific receptors are generally divided into three classes: mu opioid receptors (MORs), delta opioid receptors (DORs), and kappa opioid receptors (KORs), although only the MORs and KORs are associated with

addiction treatment. Each opioid receptor is connected to a G-protein pathway that allows them to produce various responses (Cong et al., 2015).

MORs are found in the mesocorticolimbic region of the brain where they affect the dopaminergic pathway (Kudo et al., 2014). The most common endogenous ligands for mu opioid receptors are enkephalin and the beta-endorphins, inhibitory molecules that are linked to the perception of pain. Neurons in the bed nucleus of the stria terminalis (BST) produce and release the endogenous opioid enkephalins. The enkephalins travel to the ventral tegmental area (VTA) where MORs are located on the plasma membranes of neurons that produce gamma-Aminobutyric acid (GABA). The binding of enkephalin to the MOR decreases the release of GABA and increases the release of dopamine, producing a high (Kudo et al., 2014).

KORs work primarily with dynorphins and enkephalins. The ligand receptor system modifies emotions in response to pain (Cahill et al., 2014). KORs are the driving force behind the stress response and negative changes in mood that are often associated with long term pain. This is primarily because the activation of KORs leads to a decreased release of dopamine in the stress pathway of the brain (Sigpa, Lintas, & Diana, 2008). The KORs are the link between the psychological and physiological effects of opioids, and the KOR system is thought to be heavily involved in reward responses associated with opioid addiction (Cahill et al., 2014).

While there are different types of opioid receptors, there are also different types of molecules that bind to the receptors. Aside from being classified as either endogenous or exogenous, opioid ligands can be separated into agonists and antagonists. According to the *McGraw-Hill Dictionary of Scientific and Technical Terms*, an agonist is a molecule that binds to a receptor and activates it, producing a response. All the molecules discussed above are agonists, and the response they produce is pain relief by inhibiting the pain pathway or stress elevation by activating the stress pathway. Antagonists, on the other hand, work to decrease the response of the receptors. When an antagonist binds to a receptor, it does not activate the receptor and does not create any response. In this case, antagonists cause pain to hurt more, but they decrease stress felt.

Despite their different roles in the body, agonists and antagonists do have one thing in common: they can both be used to treat opioid addictions. Agonists are used to avoid opioid withdrawal symptoms. Certain agonistic drugs can produce effects similar to those of heroin,

without producing the euphoric high. Antagonists are used to block heroin from reaching the MOR or KOR. With an antagonist in the body, heroin is rendered useless.

Because they differ in structure and properties, both agonists and antagonists have distinct advantages and disadvantages as addiction treatments. Therefore, it is now widely believed that an addiction treatment which utilizes both agonistic and antagonistic properties provides the most efficient addiction recovery process.

## Discussion

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Agonists can produce a wide variety of effects. The pain relief caused by morphine is seemingly mild compared to the euphoric highs that heroin is capable of. This range of effects is due to the many different structures that agonists have. The structure of an agonist dictates how quickly it will enter the brain, how tightly it will bind to the MOR, and ultimately what responses it will produce in the body.

Heroin and morphine are both common agonists, and each one produces a specific response. In this example, the key is the fact that heroin is metabolized before it enters the brain, while morphine is not. When heroin enters the body it is broken down into 6-monoacetylmorphine (6-MAM), in a process known as deacetylation. The 6-MAM is then further metabolized into morphine at a later time (Seleman et al., 2014).

After metabolism, the 6-MAM is able to enter the brain through a P-glycoprotein (P-gp), which is regulated by a selective PSC833 inhibitor that is endogenous to the brain (Seleman et al., 2014). Opiate drugs like morphine that do not need to be metabolized go directly to the glycoprotein after injection. While the PSC833 inhibitor increases the passage of agonists like morphine into the brain, it does not have any effect on the transport of 6-MAM. Therefore, morphine can only travel efficiently when the P-gp is inhibited by the PSC833. On the other hand, 6-MAM is always able to enter the brain, as shown in the graph below (Seleman et al., 2014). This helps explain why heroin is much more potent, producing more intense highs at much smaller doses (Seleman et al., 2014).

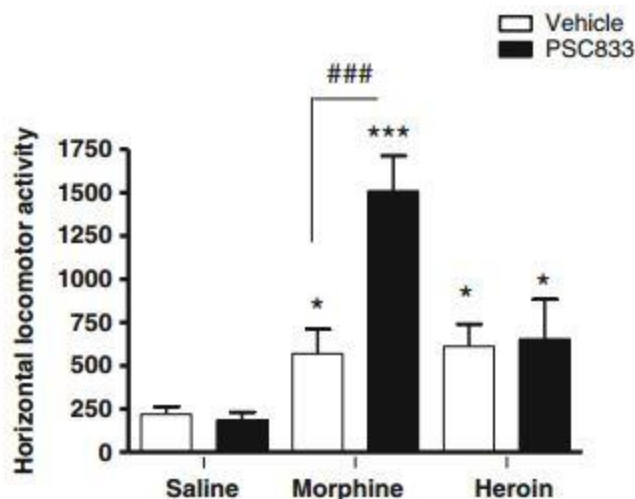


Figure 1. Effects of P-gp inhibition by the PSC833 on the transport of molecules. The black bars show the amount of PSC833 activity that is needed to transport a certain amount of a molecules, shown by the white bars, into the brain. The saline shown is used as a control group (Seleman et al., 2014).

After agonists pass through the brain, they bind to the MOR. In the receptor, they form very stable bonds with D147 and H297 amino acid sites (Cong et al., 2015). The importance of these bonds has led the H297 site to be referred to as the “opioid anchor.” (Cong et al., 2015). The strong hydrogen bond interactions formed at the H297 and D147 sites are able break interactions between the R165 and T279 sites. The dissolution of these bonds changes the shape of the receptor, moving the transmembrane 6 (TM6) protein subunit, which contains the T279 site, closer to the transmembrane 3 (TM3) subunit and the R165 site. This shape change, as seen in the figure below, makes the MOR temporarily active (Cong et al., 2015).

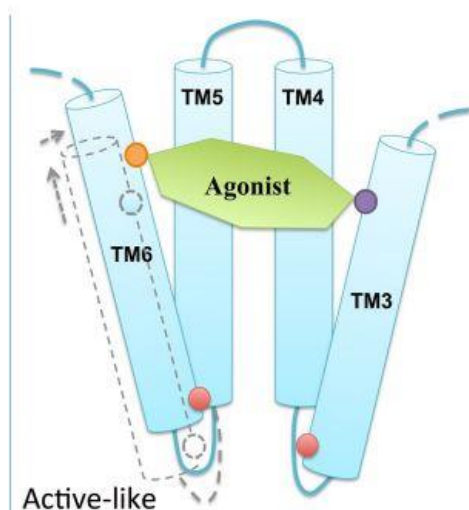


Figure 2. Agonist binding to a MOR. The orange and purple dots denote the H297 and D147 amino acid sites respectively, and the red dots show the T279 (left) and R165 (right) sites. The dotted outline shows the position of the TM6 before agonist binding (Cong et al., 2015).

While all agonistic binding results in a change of shape in the MOR, the specific number and types of bonds formed between the D147 and H297 sites vary, depending on the structure of the agonist (Cong et al., 2015). The figure below shows the difference between morphine and hydromorphone (HMP), another opioid agonist, in the way that they bind to the receptor. Morphine uses a direct hydrogen bond at the H297 site, while HMP uses many water-mediated hydrogen bonds. The direct bond that morphine uses is stronger; it causes a more pronounced change in the shape of the MOR and results in a larger response (Cong et al., 2015).

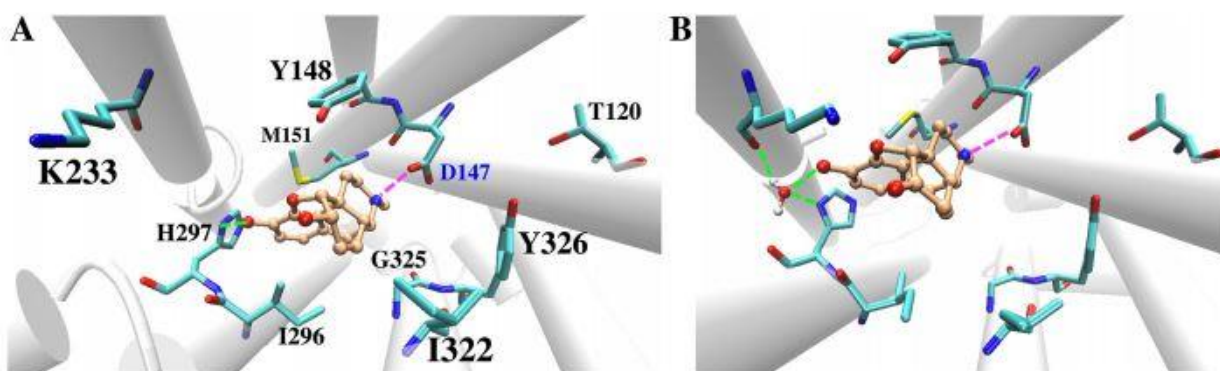


Figure 3. Differences in MOR binding between morphine (A) and HMP (B). The ligand is the orange colored molecule. Interactions with the H297 site are shown by green dotted lines. Interactions with the D147 site are shown by purple dotted lines (Cong et al., 2015).

When an agonist binds to a mu opioid receptor located on a GABAergic neuron in the ventral tegmental area (VTA), the receptor's change in shape activates a G-protein pathway that halts the production of the GABA neurotransmitter (Chartoff et al., 2014). As seen in the figure below, the binding of an agonist causes a G-protein to shut down calcium ion channels that allow  $\text{Ca}^{2+}$  to enter the neuron and open potassium channels that pump  $\text{K}^{+}$  out of the neuron. The G-protein also deactivates the adenylate cyclase enzyme, which is required to produce cyclic adenosine monophosphate (cAMP). When cAMP concentration is decreased,  $\text{I}_h$  cation currents in the neuron are deactivated. These changes cause the neuron to become more negative, making it harder to initiate an action potential and thus decreasing the release of GABA (Chartoff et al., 2014).



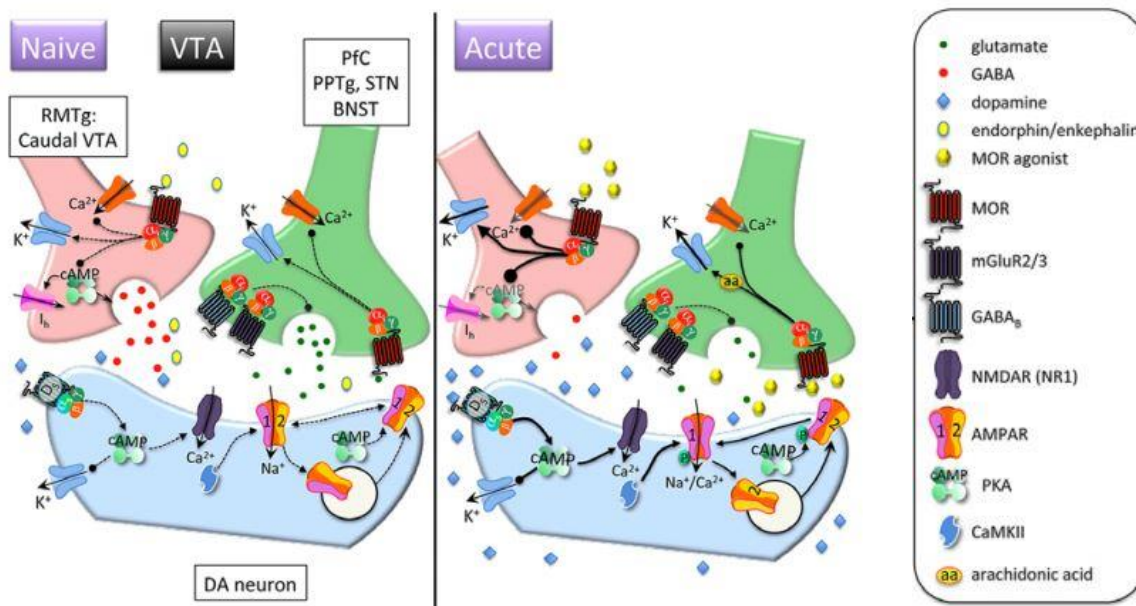


Figure 4. The effect of MOR agonists on GABAergic neuron and dopaminergic neuron interactions. The diagram on the left shows the normal interactions in the VTA. The red GABAergic neuron releases GABA (red dots) that inhibits the blue dopaminergic neuron. The diagram on the right shows the presence of MOR agonists, in this case, morphine is represented by the yellow ovals. Less GABA is synthesized, allowing more dopamine (blue triangles) to be released. The green neuron represents Glutamatergic neurons that are also present in the VTA. (Chartoff et al., 2014).

Agonist structure plays a big role even after the opioid has bonded to the MOR. (Seleman et al., 2014). Agonists that form strong bonds, such as morphine, release more dopamine for a longer period of time, as compared to weaker agonists like HMP. Also, the PSC833 inhibitor at the entrance to the brain has been shown in some cases to have the ability to change the intensity of the response that an agonist like morphine produces (Seleman et al., 2014).

Despite structural differences, all opioid agonists create a lack of inhibitory GABA molecules in the VTA. This stops the inhibition of dopaminergic neurons and allows the release of dopamine (Haile, Kosten & Kosten, 2008). The resulting flood of released dopamine is the cause of the characteristic opioid high. The dopamine primarily affects the frontal regions of the brain, specifically the nucleus accumbens and the prefrontal cortex. Unsurprisingly, these regions are known to have an important role in the addiction process (Haile, Kosten & Kosten, 2008).

While opioid receptor agonists are known for causing these highs that lead to addictions, they can also be used to help recovering addicts. Agonists are often used to relieve withdrawal symptoms. They can stop the feelings of sickness or dizziness without causing the dangerously

addictive highs. Of all the agonists used for opiate addiction treatment, methadone has proven to be the most successful.

Methadone maintenance treatment (MMT) was first approved in the 1960s and soon became one of the most widespread and effective methods for treating opiate addiction (Bart, 2012). Methadone, pictured below, works by stabilizing the mu opioid receptor post-heroin use. When methadone binds to the MOR, it activates the G-protein a little differently. Methadone causes the G-protein to activate protein transcription factors that changes which proteins are being created in the neuron. Using this process, methadone can slowly reverse the effects of heroin abuse (Toskulkao et al., 2010). This effect is illustrated by the fact that methadone can decrease the tolerance to heroin that the body has developed.

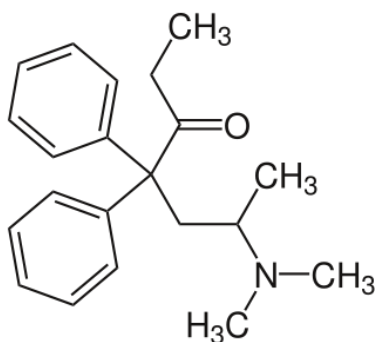


Figure 5. Structure of methadone

When addicts keep using heroin, the body acknowledges the increased concentrations of opioid ligand and responds by producing more mu opioid receptors (Toskulkao et al., 2010). This increase in receptor number makes the addict more tolerant to heroin, since they need a larger dose to fill all the MORs. Studies have shown that methadone regulates the production of MORs by affecting the genes that code for the receptors. In patients receiving methadone treatments, the messenger ribonucleic acid (mRNA) molecules that provide the code for the production of MORs are decreased by about 36.6% as compared to pre-treatment levels. This means that methadone actually decreases the number of MORs in the body, as seen in the figure below. Methadone restores the receptor concentration to normal levels and decreases an addict's tolerance to heroin (Toskulkao et al., 2010).

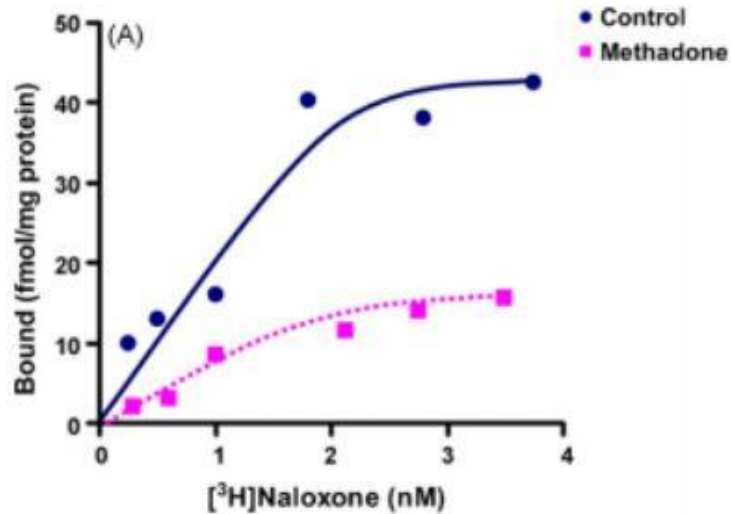


Figure 6. The effects of methadone on MOR concentration. The graph plots the amount of the antagonist naloxone introduced to the body versus the amount of naloxone that binds to a MOR. Since methadone decreases the amount of MORs present, less naloxone is able to bind (Toskulkaio et al., 2010).

Methadone can have many sociological benefits as well. The treatment allows patients to resume a fairly normal life. They are able to live at home and go to work; the only catch is that patients have to stop into a clinic every day to be tested for heroin use and to receive the next dose of methadone (Goldstein, 2001). Another disadvantage to methadone is that patients are usually unable to stop taking the medication. Patients become dependent on methadone, and ceasing to use it brings about the return of heroin withdrawal symptoms, which often leads to a heroin relapse. (Goldstein, 2001). Due to this dependency, patients on methadone are often still regarded as addicts by society.

A survey of 315 patients showed that 80% of addicts currently using methadone believe that after a certain period, patients should try to get off methadone (Stancliff et al., 2002). 36% believe that other addicts look down on those receiving methadone treatment, and 58% are unwilling to talk to friends or family members about their treatments. These negative connotations that surround methadone can lead to isolation of the patient; some methadone patients even find themselves being denied certain medical procedures such as kidney transplants (Stancliff et al., 2002).

Overall, 60% of patients will remain in a one year methadone program (Bart, 2012). However, the majority of these patients will then remain on methadone for the rest of their lives.

Unfortunately, about 15% of patients being treated with methadone will be using opiates simultaneously and are the most likely to have a relapse (Bart, 2012).

In comparison to agonists, antagonists have vastly different properties, but have also had a lot of success in the treatment field. Antagonists bind to MORs in a way that blocks the response that heroin or other opiates produce. Antagonists shut down the opioid's signaling pathway and stop the body from responding to opioids agonists like heroin.

Antagonists bind to the same H297 and D147 sites as agonists do; however, antagonists use a pattern of hydrogen bonds at the H297 site that is much weaker than the interactions used to anchor agonists (Cong et al., 2015). As a result of these weaker interactions, antagonists are not able to break the hydrogen bonds that are holding the T279 and R165 sites together. Therefore, these hydrogen bonds between the T279 and R165 sites stabilize the structure of the MOR in an inactive position, as seen in the figure below (Cong et al., 2015).

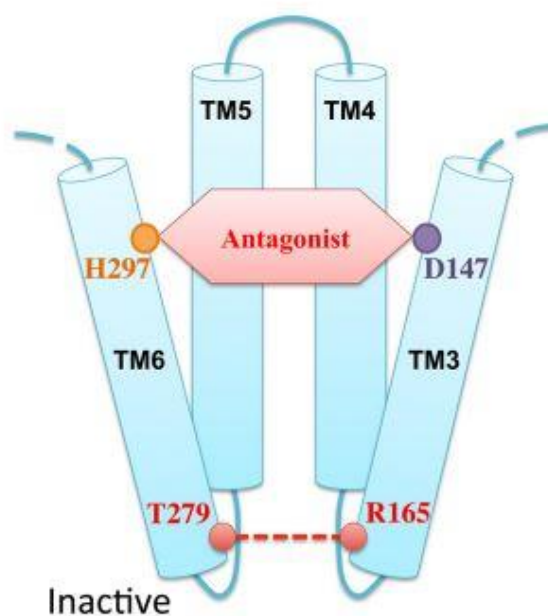


Figure 7. Antagonistic binding to MORs. The dotted red line shows hydrogen bonding between the T279 site and the R165 site that keeps the receptor in an inactive position (Cong et al., 2015).

Since antagonists do not change the shape of the MOR, G-proteins are not activated. As seen in the figure below (Chartoff et al., 2014). cAMP production continues, potassium pumps stay inactive, calcium channels remain open, and  $I_h$  cation currents continue to flow. The interior of the GABAergic neuron remains positive, allowing action potentials to release GABA that then binds to and inhibits dopaminergic neurons (Chartoff et al., 2014).

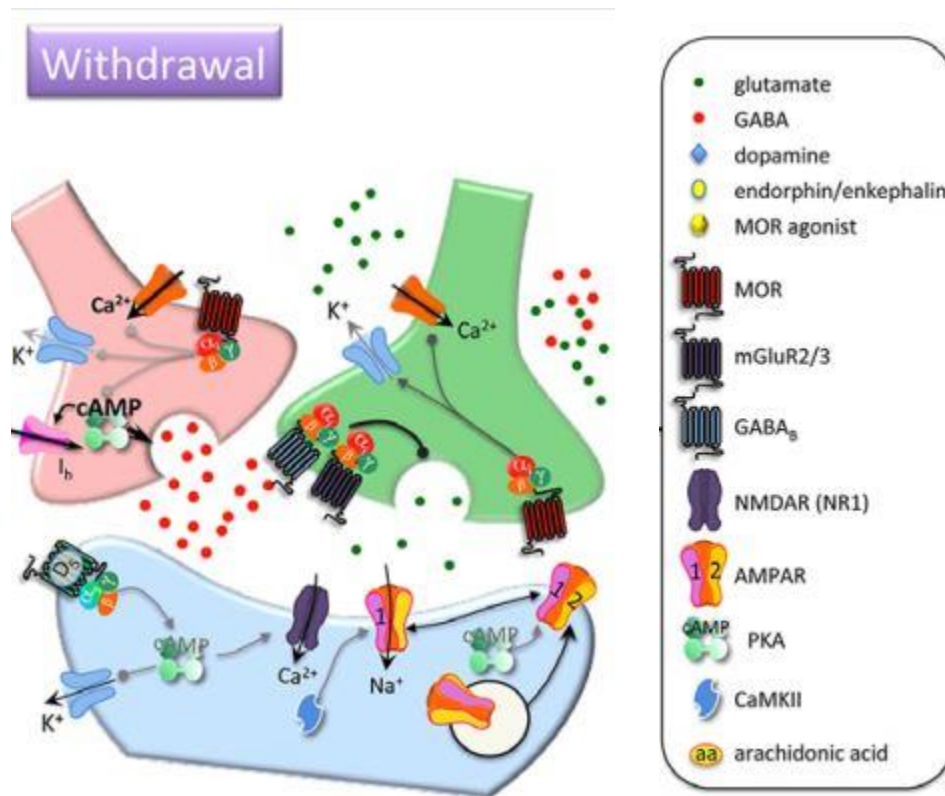


Figure 8. Antagonistic interactions in the VTA. Antagonists block the effects of opioid agonists, inducing withdrawal.

Calcium channels and cation currents continue to work in GABAergic neurons (shown in red). Therefore, large amounts of GABA (red dots) are released, which significantly decreases dopamine (blue triangles not shown) production by the blue dopaminergic neuron. The neuron in green represents glutamatergic neurons that also regulate dopamine release in the VTA (Chartoff et al., 2014).

The main antagonist used for opioid addiction treatment is naltrexone, pictured below. When naltrexone is present in the body, it uses the process described above to keep the interior of the GABAergic neurons positively charged. However, when agonists like heroin are introduced, they create a response that leads to a negatively charged interior. Therefore when heroin is used in the presence of naltrexone, the effects of naltrexone and heroin negate each other, rendering heroin useless. When a patient is taking naltrexone, they can inject all the heroin they want, but they will not experience the highs or any of the other pleasurable effects (Goldstein, 2001).

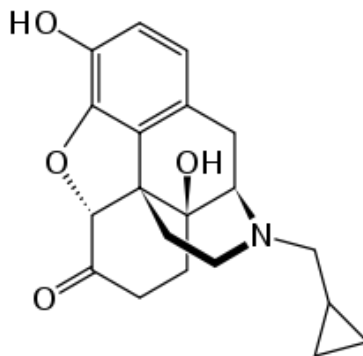


Figure 9. Structure of naltrexone.

While naltrexone can block the effects of opiate agonists, it cannot stop the withdrawal symptoms felt by the addict during the treatment (Van Bockstaele et al., 2008). However, the timing of naltrexone administration can cause a slight decrease in the intensity of withdrawal symptoms. Naltrexone treatments can be implemented when an addict has already stopped using opiates, and therefore is already in the withdrawal period. Naltrexone can also be taken while opiates are still in the addict's system, in which case naltrexone's antagonistic properties negate the effects of all opiates and induce withdrawal in an addict (Van Bockstaele et al., 2008).

When an individual is going through opiate withdrawal, norepinephrine begins to flood the brain, causing withdrawal symptoms such as shivering, shaking and diarrhea (Van Bockstaele et al., 2008). Though naltrexone cannot stop this spike in norepinephrine levels, using naltrexone to induce withdrawal can decrease the magnitude of norepinephrine released and withdrawal symptoms felt, as shown in the figure below (Van Bockstaele et al., 2008).

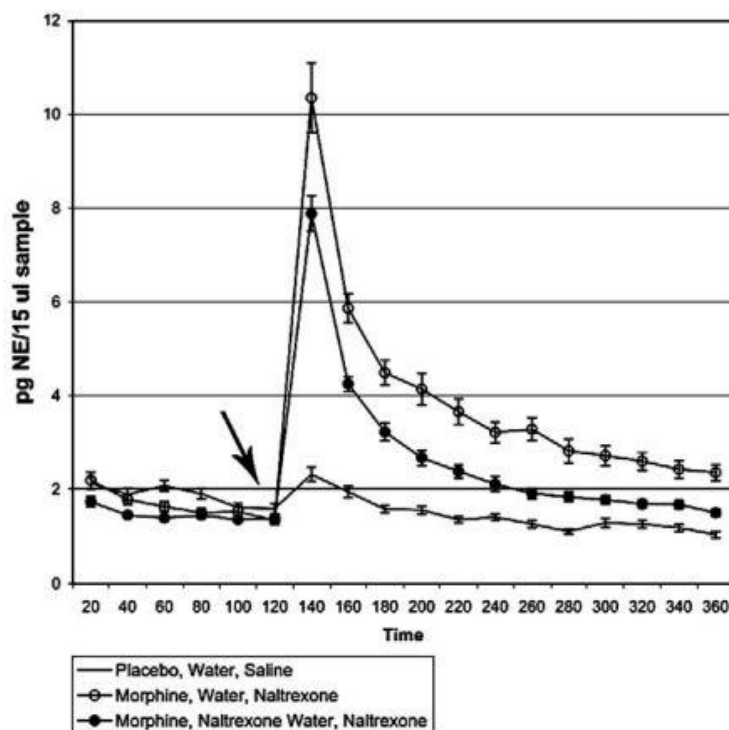


Figure 10. Effects of naltrexone on the amount of norepinephrine released in morphine addicted rats. The open dots show the effects of naltrexone (added at the arrow) when the addict is already going through withdrawal. The closed dots show the norepinephrine released when withdrawal is induced by naltrexone added to the rats' drinking water. The blank line shows the control group. (Van Bockstaele et al., 2008).

Naltrexone cannot stop withdrawal symptoms the way that methadone can. The principle behind naltrexone is that it conditions addicts to stop using heroin (Kunøe et al., 2010). Addicts on naltrexone continue to crave heroin. However, when this craving leads to heroin use, the opiate produces no effect. After enough times of taking heroin with no euphoria, the theory is that addicts will stop associating heroin with highs, which will eventually cause them to stop craving heroin or seeking it to mitigate their withdrawal symptoms (Kunøe et al., 2010).

However, heroin cravings often get bad enough that they cause patients to stop using naltrexone. Since patients know that giving up naltrexone will produce the high that they desire, it is very easy for them to stop using the antagonist in favor of heroin. Although the number of patients who quit naltrexone is not easily determined, a strong indication of this number is seen by looking at patients who "challenge" naltrexone.

As the graph below shows, many patients still try to use heroin while on naltrexone (Kunøe et al., 2010). The patients are said to be “challenging” naltrexone; they are craving heroin and are curious to see if naltrexone can really stop heroin’s highs. This challenging behavior ideally should decrease the longer the patient is on naltrexone, eventually resulting in no heroin use. However, many patients find that their willpower weakens over time and will challenge naltrexone more toward the end of the treatment (Kunøe et al., 2010).

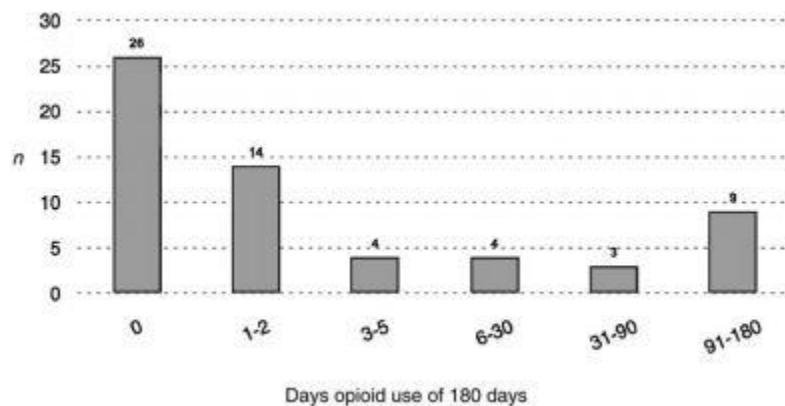


Figure 11. Number of naltrexone patients who used heroin or other opiates over a treatment period of 180 days. (Kunøe et al., 2010).

Of the 60 patients used in this study, about 56% challenged naltrexone over the six month period, while a quarter of the patients used opioids repeatedly while on naltrexone (Kunøe et al., 2010). Historically, this does not bode well for the probability of these patients remaining in treatment. While these studies forced the use of naltrexone over the entire six month period, in real life situations it is much harder to find the motivation to stay on naltrexone (Kunøe et al., 2010).

Another downfall to naltrexone is the fact that it may not block all doses of heroin (Kunøe et al., 2010). When patients challenge naltrexone, it leads them to try higher and higher doses of heroin in hopes of getting a response. These larger doses increase the chances of a heroin molecule binding to a MOR instead of a naltrexone molecule binding to a MOR. 61% of the patients who used opiates while on naltrexone reported that they felt no high, but 12% of the opiate users reported that they felt a full high at least some of the times they used opiates (Kunøe et al., 2010). Unfortunately, these highs only reinforce the challenging behavior and eventually convince patients to stop taking naltrexone.



While methadone and naltrexone both have their strengths, they also have weaknesses that can lead to relapsing. To fill in the gaps that both agonist treatments and antagonist treatments have, a treatment has been developed that combines the two methods. Buprenorphine (BUP), pictured below, acts as both an agonist at mu opioid receptors and a partial antagonist at kappa opioid receptors (Haile, Kosten & Kosten, 2008). It is just like methadone in the way it gives relief from withdrawal symptoms and facilitates the return of normal physiological functioning, but BUP also blocks negative effects, such as stress, caused by further opioid use (Bart, 2012).

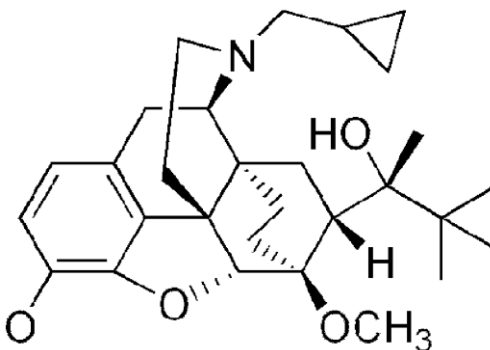


Figure 12. Structure of buprenorphine

The key to BUP's success is the fact that it blocks the kappa opioid receptor rather than blocking the mu opioid receptor (Spiga, Lintas & Diana, 2008). The antagonism of the KOR halts the stress response that often accompanies withdrawal (Knoll et al., 2007). This decreased stress response is thought to help retain many brain functions, such as memory storage and decision making, as well as decreasing stress (Knoll et al., 2007). This can ultimately help speed up recovery and lessen withdrawal's side effects (Spiga, Lintas & Diana, 2008).

Studies have tested the effects of KOR agonists in order to understand the KOR's role in rats' fear response (Knoll et al., 2007). A stressful situation leads to the activation of a cAMP dependent transcription factor called the cAMP-response element binding protein (CREB). The CREB then induces the synthesis of dynorphins by initiation the transcription of certain genes. The excess agonistic dynorphins then flood the nucleus accumbens where they bind to the KORs (Knoll et al., 2007).

The dynorphins, kappa opioid receptors agonists, bind in a way very similar to MOR binding. The KOR is coupled with a G-protein in a dopaminergic neuron (McLaughlin et al., 2004). Agonist binding causes a change in the KOR's structure that activates the G-protein. The

G-protein in turn activates a G-protein dependent kinase. The kinase is then responsible for the phosphorylation of proteins that help create an action potential in the dopaminergic neuron and lead to the release of dopamine, thus creating a stress response (McLaughlin et al., 2004).

Just like antagonistic MOR binding, when an antagonist like buprenorphine binds to the KOR, the G-protein is not activated since there is no change in the shape of the receptor. The halted pathway stops the release of dopamine and inhibits the stress response. This lowering of stress is part of the reason that KOR antagonists like buprenorphine are so effective, considering that stress is one of the major factors that can lead to drug seeking and ultimately a relapse (Sedki et al., 2014).

One study showed the effects of KOR antagonists on drug seeking behavior in rats (Sedki et al., 2014). Over a period of ten days, the rats were conditioned that pressing an “active” lever would dispense heroin, while an “inactive” lever would not. The rats then went through food-deprivation in order to expose them to stress. As seen in the charts below, the rats that received the KOR antagonist norbinaltorphimine (norBNI) used the active lever less while in the food-deprivation period. This supports the idea that the norBNI decreased the stress response in the rats, therefore reducing that rats’ tendency to use heroin (Sedki et al., 2014).

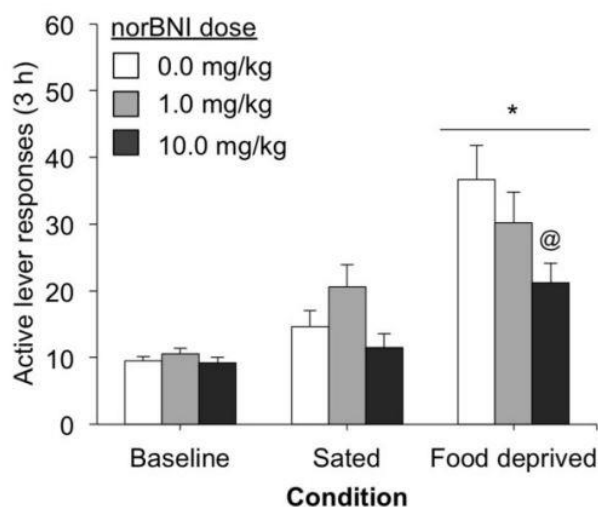


Figure 13. Graph showing the number of times rats pressed the active lever to dispense heroin. Baseline shows the number of times each group of rats pressed the lever before any norBNI was added. The “sated” column measures the number of times the lever was pushed when the rats had received norBNI, but were not under stress. The “food deprived” column shows the number of times the lever was pushed when the rats received norBNI and were under stress. This last column shows how KOR antagonism decreases the stress response. (Sedki et al., 2014).

However, due to variations in structure and location, only KOR antagonism lessens the stress response (Sedki et al., 2014). When the same experiment was repeated using naltrexone, an effective MOR antagonist, the number of times the active lever was pushed actually increased, as shown below. This indicates that naltrexone can actually increase the stress response, which is most likely another factor that contributes to the high relapse rates among naltrexone patients (Sedki et al., 2014).

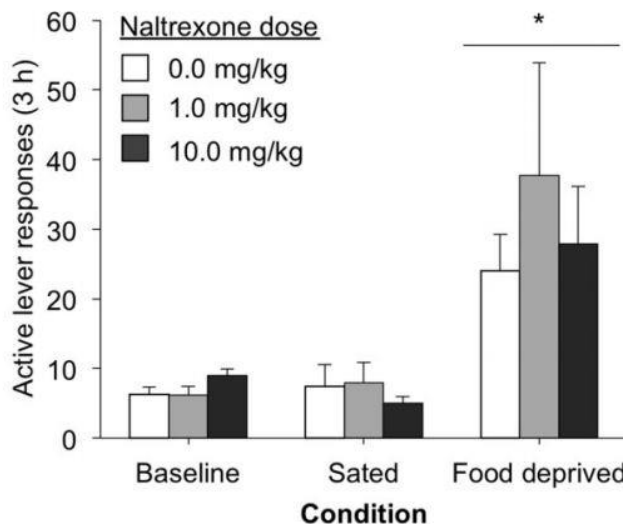
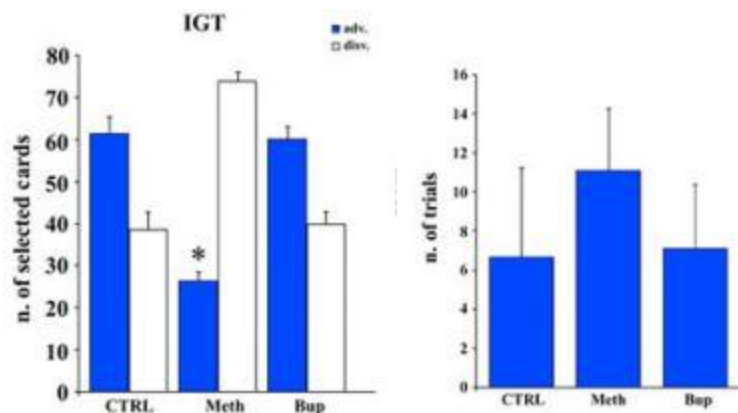


Figure 14. Effects of naltrexone on the stress response. The figure graphs the number of times the active lever was pushed under different conditions: baseline (no naltrexone, no stress), sated (naltrexone, no stress), and food deprived (naltrexone and stress) (Sedki et al., 2014).

Buprenorphine, as a partial KOR antagonist, displays these same stress reducing effects. This property can not only decrease the chance of a relapse, but it can also preserve certain brain functions as opposed to other opioid treatments. When subjected to memory and brain function testing, BUP patients score almost identically to the non-addict control population, while methadone patients received a large difference in scores (Spiga, Lintas & Diana, 2008).

For example, as seen in the charts below, methadone patients have less decision making abilities. They made more disadvantageous choices, shown in white, and did not make as many advantageous ones, shown in blue, when completing the Iowa Gambling Task (IGT). It was also shown by the matching-to-sample test (MTS) that methadone patients need more trials before they learn and remember how to complete a task (Spiga, Lintas & Diana, 2008).



Figures 15a and 15b. 13a shows the results of the IGT test when taken by a control group, methadone patients, and BUP patients. The blue bars depict the number of advantageous cards picked, showing good, stable decisions. The white bars show disadvantageous cards picked, denoting bad or high risk decisions. 13b shows the number of trials performed until members of each group could properly complete a matching-to-sample test (Spiga, Lintas & Diana, 2008).

Due to its more effective treatment, BUP is quickly becoming the most widely used opioid addiction treatment method. Aside from its pharmacological advantages, BUP has many social benefits that attract recovering addicts (Gryczynski et al., 2013). BUP has less regulations when it comes to using it; this can reduce the stress on patients, as they are able to meet in a more comfortable office setting and pick up prescriptions from a pharmacy, receiving their treatments sooner and more discretely. Also, doses of BUP are stronger and therefore do not need to be taken as frequently, which causes significantly less interruptions in the patient's life (Gryczynski et al., 2013).

BUP is preferred over naltrexone because it alleviates withdrawal symptoms as well as decreasing the stress response. These pharmacological effects, plus BUP's social benefits, cause patients to prefer BUP over methadone as well. A recent study surveyed patients to ask them why they chose a BUP treatment over methadone. Patients were given a series of options pertaining to BUP and methadone and were asked which ones were the most influential in their decision. As the table below shows, many patients turned to BUP because they believed it to be better for them physically (Gryczynski et al., 2013).

**TABLE 2.** Importance of reasons for choosing buprenorphine over methadone among new admissions to treatment with buprenorphine (*n* = 80)

	Not at all important %	A Little important %	Very important %
<b>Positive buprenorphine experiences (self and others)</b>			
You heard good things about buprenorphine and thought it may work for you	10.0	16.3	73.8
You know people on buprenorphine who have been successful	8.8	22.5	68.8
You tried buprenorphine on the street and it worked	15.0	11.3	73.8
<b>Treatment delivery structure</b>			
You get take-home doses sooner with buprenorphine	68.8	10.0	21.3
The rules at methadone programs are too strict	91.3	1.3	7.5
Methadone programs are too crowded	85.0	10.0	5.0
There is too much counseling with methadone treatment	88.8	6.3	5.0
Methadone treatment is too expensive	88.8	3.8	7.5
<b>Pharmacological and health effects</b>			
You don't like how methadone makes you feel	25.0	15.0	60.0
Methadone is bad for you physically	5.0	10.0	85.0
The withdrawal from methadone is worse than with buprenorphine	8.8	13.8	77.5
You have to stay on methadone too long	35.0	12.5	52.5
<b>Methadone stigma</b>			
People on methadone aren't really clean	46.3	20.0	33.8
People at methadone clinics aren't serious about recovery	58.8	22.5	18.8
Other people (like friends, family or probation/parole officers) would not want you to take methadone	56.3	12.5	31.3
You think methadone treatment is a "last resort" for people who can't stop using by any other means	53.8	20.0	26.0

Interviewer's instructions, read verbatim: "I am going to list some other reasons that people may have for choosing buprenorphine treatment over methadone. For each reason I list, please tell me if the reason was not at all important, a little important, or very important."

Figure 16. Table showing the importance of different factors that led patients to choose BUP treatment over methadone (Gryczynski et al., 2013).

BUP's and methadone's different pharmacological effects can come down to the patient's individual genetics and biochemistry and, of course, the drug's molecular structure and properties. For example, methadone is broken down by a particular liver enzyme used in the metabolism of drugs, cytochrome P3A4 (CYP3A4). BUP, on the other hand, uses a different metabolic enzyme, cytochrome P2D6 (CYP2D6) (Haile, Kosten & Kosten, 2008).

The need for different enzymes results from structural differences between buprenorphine and methadone (Coller et al., 2012). While both of the exogenous drugs require an enzyme to remove a methyl group, a process called demethylation, the specific location of the methyl group determines the specific enzyme that will catalyze the reaction. Buprenorphine, pictured below, has a methyl group attached to an oxygen atom. Methadone, on the other hand, has two methyl groups attached to a nitrogen atom. The CYP3A4 enzyme only facilitates N-demethylation, the removal of methyl groups from nitrogen atoms. The CYP2D6 enzyme catalyzes O-methylation by taking a methyl group off of an oxygen atom (Coller et al., 2012).

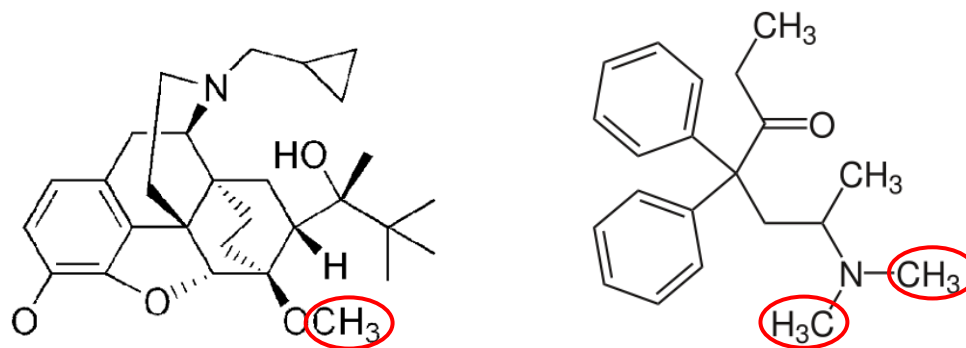


Figure 17a and 17b. Structure of buprenorphine (left) and methadone (right). Methyl groups are circled in red.

In many Caucasian populations, it is common to lack the gene that codes for the CYP2D6 needed to break down BUP (Haile, Kosten & Kosten, 2008). People who lack this gene are satisfied with methadone treatment, but often cannot metabolize normal doses of BUP due to the specificity of these enzymes (Haile, Kosten & Kosten, 2008).

This enzyme specificity can be seen in the metabolism of tramadol, an opiate painkiller similar to oxycodone (Coller et al., 2012). Tramadol is broken down into O-desmethyl-tramadol (M1) by CYP2D6 and N-desmethyltramadol (M2) by CYP3A4. As seen in the chart below, methadone patients that use the CYP3A4 enzyme produce higher levels of M2, while BUP patients that use CYP2D6 produced higher levels of M1.

	MMT	BMT	P value*	Probability score** (95% CI)
Tramadol	0.90 (0.439–1.50)	0.68 (0.049–1.28)	0.35	0.65 (0.368, 0.850)
M1	0.069 (0.057–0.113)	0.126 (0.021–0.225)	0.04	0.19 (0.061, 0.484)
M2	0.048 (0.027–0.138)	0.033 (0.003–0.061)	0.04	0.81 (0.516, 0.939)
Total recovery	0.97 (0.45–1.46)	0.74 (0.06–1.35)	0.47	0.38 (0.17, 0.66)

Figure 18. Ratios of tramadol metabolites. Numbers show the percent of the original tramadol dose that was found in urine samples as each metabolite. MMT stands for patients on methadone maintenance treatment, while BMT denotes patients on buprenorphine maintenance treatment (Coller et al., 2012).

## Conclusion

Dozens of opioids have been discovered since the first ancient use of opium from poppy plants. Each opioid has a unique structure and properties. For example, agonists activate specific receptors in the central nervous system in order to create a response. In this case, agonists like

heroin produce a high. Antagonists, on the other hand, block receptors and decrease the euphoric response.

The receptors utilized by opioids are found throughout the nervous system, and they possess various structures and functions as well. The mu opioid receptors (MORs) are primarily involved with addiction; they are responsible for heroin's characteristic highs. The kappa opioid receptors (KORs) help regulate the stress response and cognition changes that often accompany chronic pain.

While the different types of receptors can interact with the different opioids to create highs and lead to addiction, opioids and their receptors can also be used as addiction treatments for recovering addicts. By utilizing their respective properties, both agonists and antagonists can be used to treat opiate addiction. However, each type of treatment has various drawbacks. Therefore, the most effective opiate addiction treatment is a drug that combines agonistic properties with antagonistic ones.

Agonists work by changing the shape of the MOR into an active position which activates a G-protein system that inhibits GABAergic neurons and causes an increase in the release of dopamine. Though this process is essentially the same for all agonistic molecules, differences in agonist structure create slightly different responses. For example, different agonists may be able to enter through into the brain easier than others. The structure of agonists also determines how tightly the molecule binds to the MOR, which affects the intensity of the response.

Methadone is the most popular agonist used for opiate addiction treatment. Methadone prevents the symptoms of heroin withdrawal and stabilizes the body's natural functioning. For example, methadone can decrease tolerance to heroin by decreasing the number of MORs present in the body. Despite methadone's pharmacological effects, addicts find that the treatment is too disruptive to everyday life, and they do not like the thought of being dependent on another medication (Stancliff et al., 2002).

Antagonists use a different approach to addiction treatment. Antagonists bind to the MOR and change it to an inactive position. The receptor's inactive position stops the G-protein pathway. This allows GABAergic neurons to decrease the amount of dopamine released, which negates the euphoria that agonists like heroin produce.

The antagonist commonly used for opiate treatment is naltrexone. Naltrexone works at MORs to negate all the effects of heroin use. While naltrexone can induce withdrawal, it cannot

stop the symptoms felt during the process. However, due to various interactions, using naltrexone at specific stages of withdrawal can slightly reduce the symptoms. Though it can have a small effect on withdrawal symptoms, naltrexone's main function is to condition addicts so they no longer associate heroin with a high. However, patients on naltrexone often "challenge" the drug by trying opiates while on treatments, increasing the probability that they will eventually give up naltrexone in favor of heroin (Kunøe et al., 2010).

To avoid the disadvantages that methadone and naltrexone produce, scientists have developed buprenorphine (BUP). Buprenorphine is found to be much more effective because it acts as a MOR agonist and a KOR antagonist. When BUP blocks KORs, it can decrease the stress that accompanies withdrawal and better preserve certain brain functioning that makes treatment much more effective. Also, BUP is less disruptive to a patient's life because it has less frequent doses and less regulations.

Buprenorphine combines the agonistic effects of methadone with the antagonistic effects of naltrexone. Therefore, it can provide relief from withdrawal symptoms, while using antagonism at KORs, which is much more effective than MOR antagonism. The simple fact that BUP can interact with KORs instead of MORs is the key that makes the BUP treatment method a lot more successful than methadone or naltrexone. This once again supports the idea that small structural differences between opioids have a large effect on the response produced. BUP is the most effective treatment since its structure allows it to work where methadone and naltrexone cannot.



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