ABSTRACT

An Educational Guide on Opioid Structure, Function, and Their Impact on Public Health for Undergraduate Science Majors

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The opioid epidemic is a public health crisis that the United States has been facing since the 1990s and has continued to worsen during the COVID-19 pandemic. Many factors have led to the current state of the opioid epidemic, including inappropriate prescription of opioids, lack of understanding of the potential adverse effects of long-term use, opioid misuse, abuse, and dependence. The key to understanding both the addictive and analgesia qualities of opioids lies in their behavior and function in the human body on a molecular level. This thesis is an educational guide on the opioid epidemic, opioid basics, opioid receptors and cell signaling pathways, opioid alternatives, and alternative treatments for chronic pain. The purpose of this guide is to educate undergraduate science majors on opioid history, biological function, and proper use versus misuse and how they all have contributed to the current state of the opioid epidemic; awareness and education are crucial steps toward a potential solution.

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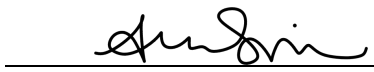

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AN EDUCATIONAL GUIDE ON OPIOID STRUCTURE, BIOLOGICAL FUNCTION, AND THEIR IMPACT ON PUBLIC HEALTH FOR UNDERGRADUATE SCIENCE MAJORS

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By

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CHAPTER ONE

Introduction to the Opioid Epidemic

In the 1990s, there was a wave of physicians prescribing opioids to their patients for chronic pain. Synthetic-opioid related deaths have been increasing since 1999, and it is estimated that between 1999-2018 almost 450,000 people have died from an opioid-related overdose, including from both illicit and prescription opioids. There are three waves of opioid overdoses that can be seen in Figure 1. The first wave was a result of the increase in physicians prescribing their patients opioids for chronic pain.[1] This correlated to Purdue Pharma introducing Oxycontin in 1996, and they aggressively promoted it to physicians, claiming that 99.3% of people would not become addicted.[2] The original marketing for Oxycontin claimed is was intended to treat chronic pain because it didn't have addictive qualities. Sales of OxyContin alone grew from $48 million in 1996 to $1.1 billion in 2000.[2] The second wave of opioid overdose deaths started in 2010, concurrent with a significant increase in overdose deaths involving heroin.[1] This was seen because by 2004, OxyContin was a leading drug of abuse in the United States.[2] Most opioid addicts that start with prescription opioids eventually end up turning to heroin because of the lower cost and higher level of euphoria they desire to achieve. The third wave began in 2013 accompanied by a rapid increase in the number of overdose deaths involving synthetic opioids, particularly those containing illicitly manufactured fentanyl.[1]

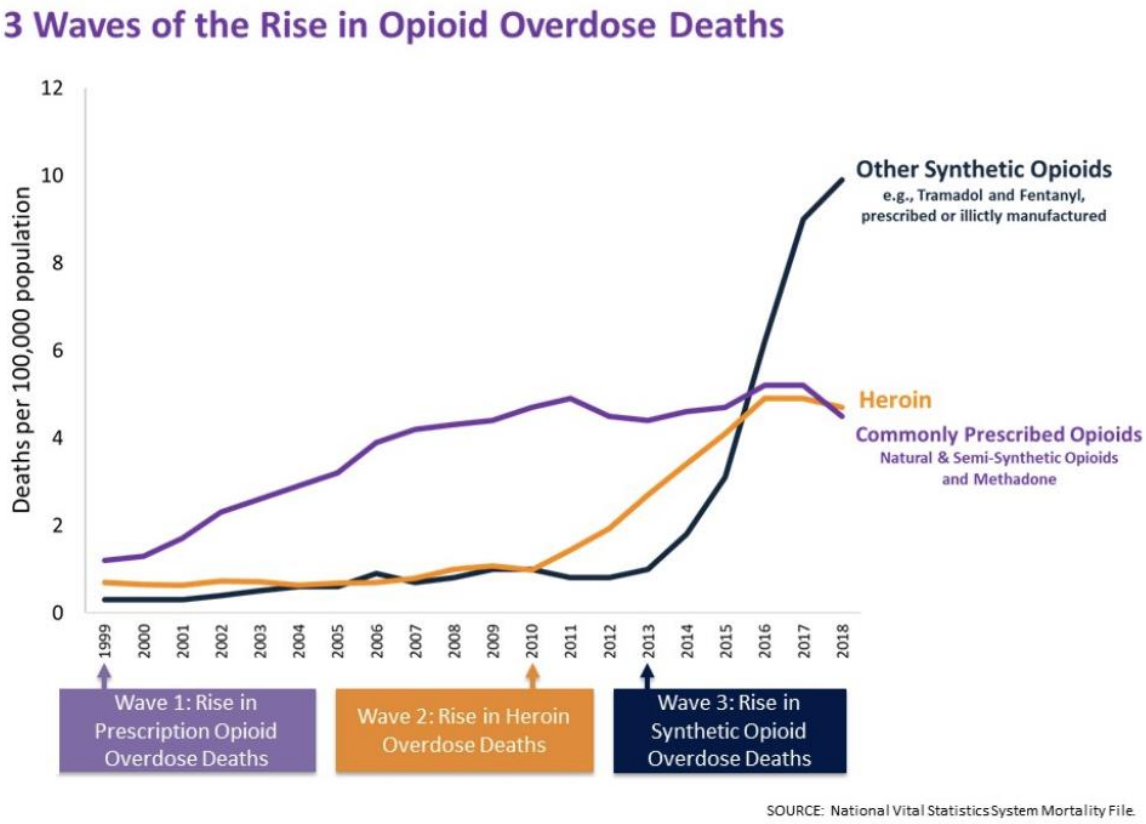

Figure 1. Three Waves of the Rise in Opioid Overdose Deaths.[1]

The majority of opioid users start their addiction with prescription medications for chronic pain. Opioids should not be used to treat chronic pain, although that was their advertised purpose in the 1990s. The opioid epidemic is a complex public health issue that the United States has been facing for decades. The factors contributing to the epidemic include: the inappropriate prescription of opioids, lack of understanding of the potential adverse effects of long-term use, opioid misuse, abuse, and dependence.[3]

The Opioid Epidemic is arguably the most profound long-term public health crisis that the United States has faced. According to the CDC, overdose deaths accelerated during COVID-19, with 81,000 drug overdose deaths in the United States alone from May 2019 to May 2020.[4] This is the highest number of overdose deaths ever recorded in

a 12-month period, showing a 38.4% percent increase from the previous 12 months.[4] While this number includes all overdose deaths, synthetic opioids, primarily illicitly manufactured fentanyl, appear to be the primary cause of the increase in overdose deaths.[4] There are 38 U.S. states with available synthetic opioid data to report. 37 out 38 of those jurisdictions reported an increase in synthetic opioid-involved overdose deaths, and 18 of those jurisdictions reported an increase of more than 50% in opioid overdose deaths.[4] There were 10 western states that even reported over a 98% increase in synthetic opioid-involved deaths during a 12-month period.[4] Also remember that these statistics only refer to those overdose deaths that are reported and recorded, and there are 12 states that aren't even considered, so one can infer that the total number of synthetic-opioid overdose deaths is even higher. The purpose of relaying these statistics is to show that while the opioid epidemic might have been around since the 1990s, it certainly is not improving; rather it is becoming worse due to the circumstances the recent pandemic has put people in.

CHAPTER TWO

Opioid Basics

Definition of an Opioid

According to the National Institute on Drug Abuse (NIH), opioids are "a class of drugs that includes illegal drug heroin, synthetic opioids such as fentanyl, and pain relievers available by prescription such as Oxycodone, Hydrocodone, Codeine, Morphine, and many others."[5] The three main functions of opioids are to reduce pain, cause sensations of pleasure, and induce sleep.[6]

Production of Opioids

The production of opioids is divided into four categories: agriculture, laboratory, laboratory and agriculture in conjunction, and in the human body. In agriculture, opioids come directly from the seeds of *Papaver somniferum* (opium poppy). For pharmaceutical use, poppy plants are grown in Australia, France, Hungary, India, Spain, and Turkey, all under supervision of the United Nations.[6] Poppy plants are also grown illegally in many parts of the world like Mexico, Central Asia, and Latin America.[6] Opium is a fluid that is obtained by cutting open poppy seeds, then hardening the material extracted from inside the seed into resin. Morphine, Codeine, and Thebaine are extracted from the resin by pharmaceutical companies.[6] Opiates are opioids that come directly from the poppy plant.[6]

Opioids that come from both the laboratory and agriculture are termed "semi-synthetic" opioids. The process is as follows: one of the three opiates are extracted from

the resin of the poppy seed (Morphine, Codeine, or Thebaine), then that opiate is modified in a laboratory to become a new type of opioid. For example, Thebaine (Figure 2) is modified to be Hydrocodone (Figure 3) by the addition of a carbonyl group, or to Oxycodone (Figure 4) by the addition of a hydroxyl group. Both are popular synthetic opioids used as pain relievers. Right before the start of the 20th century, Bayer Pharmaceuticals wanted to create new types of opioids, so they modified opiates in a laboratory. The company's first product was marketed and sold under the name "heroin" and was used to treat a cough.[6]

Synthetic opioids are made solely in the laboratory and involves no part of the poppy plant. An example of a synthetic opioid is Methadone, which is the most common pharmaceutical treatment for opioid addiction. Another example is Fentanyl, which is one of the strongest opioids, and is only used medically in hospitals to treat chronic cancer pain or for anesthesia during surgeries.[6] Illicit opioids are both grown as poppy plants, but are also produced in unauthorized labs.

The fourth source of opioids is the human body, more commonly known as endorphins, which are considered to be the body's natural opioid. Endorphins affect the experience of pain, pleasure, and reward.[6] A study done by the University of San Francisco in 2018 found that the body's natural opioids affect the brain much differently than a synthetic opioid like Morphine. Researchers thought that this discovery might help to explain why synthetic opioids are so addictive. Both synthetic and endogenous opioids produced by the brain bind to and activate opioid receptors on the surface of nerve cells.[7] What the new research reveals is that synthetic and natural opioids also activate opioid receptors inside the cells, but that the locations of those activated intracellular receptors

are different in synthetic opioids than in opioids produced by the brain.[7] This difference may explain why the rewards of synthetic opioids, and therefore their addictiveness, is much greater than opioids produced by the brain.[7]

Beta-endorphins (Figure 6) are neuropeptides whose main function is pain management. They are said to have Morphine-like effects and are involved in a number of rewards systems: feeding, drinking, sex, and maternal behavior.[8] The anterior pituitary gland is responsible for synthesizing beta-endorphins from the precursor protein proopiomelanocortin (POMC). However, many researchers suggest that the immune system is also capable of synthesizing beta-endorphins because immune cells possess the mRNA transcripts for POMC.[8] Beta-endorphins function in the peripheral nervous system (PNS) by binding to opioid receptors at pre-synaptic and post-synaptic terminals to produce analgesia. The inhibition of a key protein in the transmission of pain, tachyinins, is the product of a cascade of events brought about by the binding of beta-endorphins to opioid receptors in the PNS.[8] In the central nervous system, beta-endorphins bring about their analgesia effect by binding to the pre-synaptic terminals of opioid receptors, which inhibits the release of GABA, an inhibitory neurotransmitter, and results in the excess production of dopamine.[8] Prescription opioids like Vicodin (Figure 3), Morphine (Figure 5) and Fentanyl (Figure 7**)** are usually prescribed to patients for postoperative pain; they manage pain because they mimic natural endorphins by binding to opioid receptors in the peripheral and central nervous systems. Although they all differ in structure, they share a beta-phenylethylamine group (Figure 8), which is what allows them to bind to the opioid receptors.[8]

In a study done to understand endorphins and their importance in pain management, specifically in a postoperative environment, results showed that, "acute administration of exogenous opioids inhibits the production of endogenous opiates (e.g., beta-endorphins)."[8] This means that patients who underwent general anesthesia for an operation showed a significant increase in beta-endorphins during their operation, and the increase was inhibited by Fentanyl, which was being administered at the same time as the general anesthesia. From these results, the conclusion was drawn that, "The chronic administration of exogenous opioids inhibits the production of both endogenous opiates and mu-opioid receptors."[8] In others, the continuous supplying of opiates to the human body decreases the body's ability to produce endorphins and the receptors they bind to.

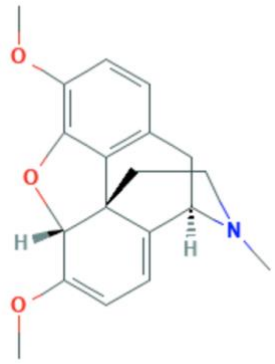

Figure 2. Chemical Structure of Thebaine ($C_{19}H_{21}NO_3$).[9]

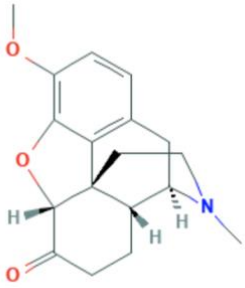

Figure 3. Chemical structure of Vicodin also known as Hydrocodone ($C_{18}H_{21}NO_3$).[10]

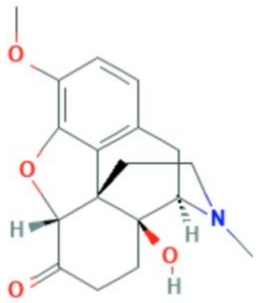

Figure 4. Chemical structure of Oxycontin also known as Oxycodone ($C_{18}H_{21}NO_4$).[11]

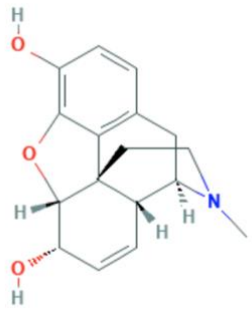

Figure 5. Chemical Structure of Morphine ($C_{17}H_{19}NO_3$).[12]

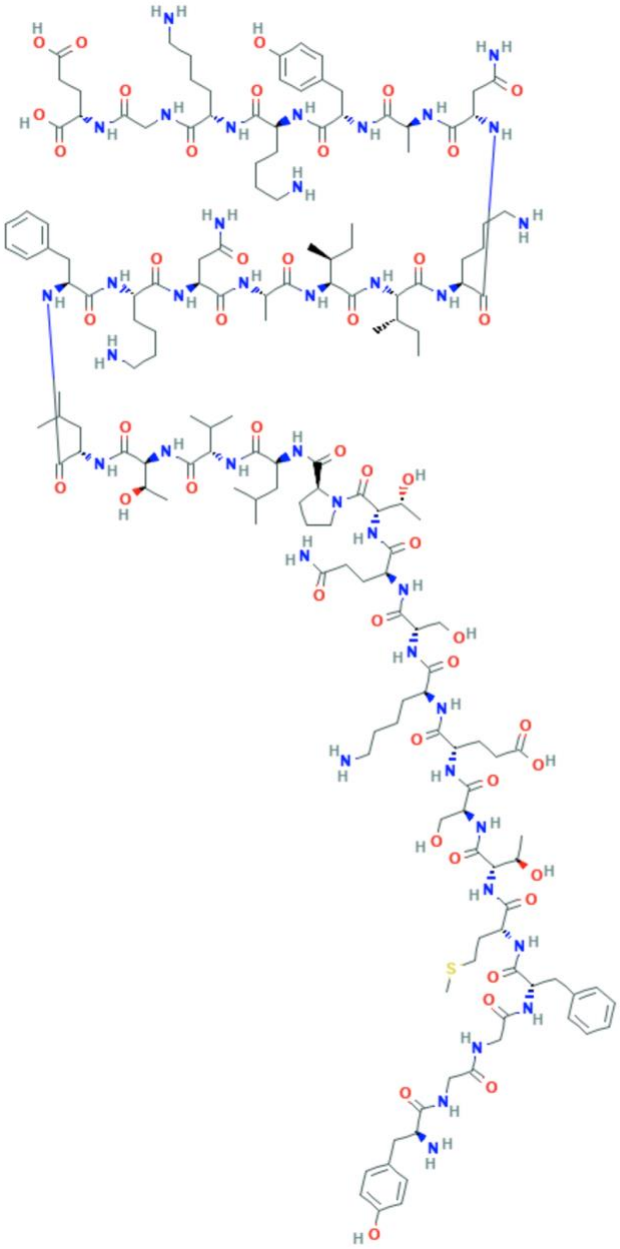

Figure 6. Chemical structure of a beta-endorphin known as beta-lipotropin, a protein-derivative ($C_{158}H_{251}N_{39}O_{46}S$).[13]

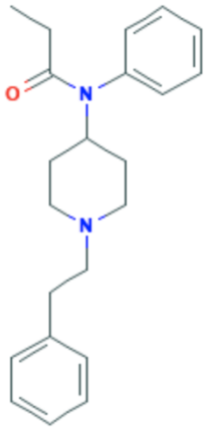

Figure 7. Chemical Structure of Fentanyl $C_{22}H_{28}N_2O$).[14]

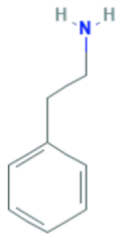

Figure 8. Chemical structure of Phenethylamine, as a group a bond replaces one of the hydrogens directly bonded to the nitrogen.[15]

Effect of Opioids on the Brain

Four areas are discussed when looking at how opioids affect the brain: pain, alertness and breathing, pleasure, and memory.[6] The different effects that opioids have on the brain can be attributed to opioids binding to and activating opioid receptors in different parts of the brain.[6]

Opioids are most associated with their ability to mitigate the sensation of pain. Opioids achieve this by binding to specific opioid receptors both in the brain and spinal cord, which causes a change in how the pain signals are transmitted and processed.[6]

Opioids bind to opioid receptors in the brainstem, which causes a reduction in breathing and alertness. This is a characteristic of opioids that is utilized by medical professionals because it allows anesthesiologists to use opioids to put patients to sleep. On the other hand, this characteristic of opioids is what makes them likely to cause a lethal overdose. When a person overdoses on opioids it can reduce their breathing rate to an alarmingly low level, in some cases completely stopping a person from breathing.[6]

Opioids alter the perception of pleasure by targeting the brain's reward pathway. They achieve this by binding to and activating receptors that results in the release of dopamine, which leads to a sensation of pleasure or reward. Endorphins, which are termed the body's naturally produced opioids, also results in the release of endorphins. The difference is that pharmaceutical and illicit opioids cause a much larger amount of dopamine to be released, which is why the perception of pleasure is so much more intense than with endorphins.[6]

Perhaps one of the more fascinating effects of opioids is how they impact memory. Opioids bind to and activate receptors in the brain which results in the release of dopamine. They can also bind to neurons associated with memory, causing an association between a person's surroundings and the sensations of intense please felt after using an illicit or pharmaceutical opioid.[6]

Effect of opioids on the Body

According to the National Institute on Drug Abuse the possible short-term health effects of opioids are pain relief, drowsiness, nausea, constipation, euphoria, slowed breathing, and death. When misused, the possible long-term health effects are increased

risk of overdose or addiction if misused. If opioids are used while pregnant then there is a risk of miscarriage, low birth weight, and neonatal abstinence syndrome.[16]

Opioid receptors are found in the skin, eyes, nasal passages, lungs, bones, and gastrointestinal tract, in addition to the brain and spinal cord.[6] The general effect of opioids throughout the body is to slow or inhibit processes.[6] Side effects of opioids include: constipation, dry eyes, dry mouth, lowered sex drive, and difficulty urinating.[6]

Opioids Forms and Different Types of Opioids.

Opioid function is crucial to both their immediate effect on the brain and long-term effects on reward pathways in the brain. Opioids can be administered through many different forms as can be seen in the "common forms" column in Table 1. "The faster an opioid gets to the brain, the greater the chance it will lead to an addiction."[6] The fastest ways for an opioid to reach the brain include: injection, spraying into the nasal cavity, and inhalation through the lungs.[6] Due to this, it can be inferred why it is easier for someone to become addicted to heroin, a commonly injected illicit opioid, than a prescription oral opioid like Hydrocodone, although both forms of opioid are extremely addictive.

There are 18 types of opioids on the market for the treatment of pain in the United States.[6] A common misconception is that is that these prescription pain pills are purely made of opioids. Some of the 18 opioids that are marked in the U.S. are mixed with other medications but are still contained within the same pill. A Percocet® pill contains the opioid Oxycodone and also acetaminophen, an active ingredient in Tylenol.[6] The purpose of combining these opioids and other medications into the same pill is to attain a greater pain relief than either of the medicines alone.[6] The downside to combining these two

different types of medications in one pill is that tolerance is developed to the effects of opioids is developed, but not to the effects of its companion drug. This is dangerous because an increase of the companion drug may have serious side effects. For example, a person may increase their daily intake of Percocet® because their body has developed a tolerance to the amount of Oxycodone they had previously been taking. Unfortunately, this means there is also an increase in the amount of acetaminophen ingested, which if too much is taken then they are at risk for severe liver failure.[6]

Research has shown that administering Morphine Sulfate Immediate Release (MSIR) has similar analgesic effects to oxycodone with the exception of resulting in a lesser degree of euphoria and reward. One might infer that there is not as great habit-forming risk that comes with Oxycodone.[17] In 2017, a three-year study began with the intent of finding out of there was a way to reduce the utilization of highly euphoric opioids like oxycodone.[17] 80 participants enrolled in the study, with a mean age between 41 and 46. They were split into two groups: (1) 40 patients randomized to Morphine Sulfate Immediate Release, (2) 40 randomized to Percocet®. Each patient's numerical rating scale (NRS) pain score was measured after 60 minutes of administration of either MSIR or Percocet®.[17] The difference between the mean pains scores of the two group was 0.0 after 60 minutes. After 60 minutes, the patients that received MSIR pain scores improved from 8.3 to 4.4, while those who were administered Percocet® improved from 8.7 to 4.7. In conclusion, no clinically meaningful differences in the mean NRS pain scores between the MSIR group and Percocet® group were observed at or after 60 minutes of administration of the respective medications.[17] This was a small study, so no major conclusions can be drawn; however, it does suggest the result of prescribing less

euphoric opioids, like MSIR instead of Oxycodone, should be investigated further, especially if they both achieve the same pain relieving effect.

Commercial Names	Common Forms	Common Ways Taken	Street Names
Codeine (various brand names)	Tablet, capsule, liquid	Injected, swallowed (often mixed with soda and flavorings)	Captain Cody, Coties, Schoolboy, *With soft drinks/candy:* Lean, Sizzurp, Purple Drank *With hypnotic sedatives:* Doors & Fours, Loads, Pancakes and Syrup
Fentanyl (Actiq®, Duragesic®, Sublimaze®)	Lozenge, sublingual, tablet, film, buccal tablet	Injected, smoked, snorted	Blonde, Blue Diamond, Snowflake, Humid, Jackpot, Murder 8, Tango and Cash, TNT, White Ladies *With heroin:* Birria *With heroin pills:* Facebook
Hydrocodone or dihydrocodeinone (Vicodin®, Norco®, Zohydro®, *and others*)	Capsule, liquid, tablet	Swallowed, snorted, injected	Vikes, Veeks, Idiot Pills, Scratch, 357s, Lemonade, Bananas, Dones, Droco, Lorries, *With valium and vodka:* Triple V
Hydromorphone (Dilaudid®)	Liquid, suppository	Injected, rectal	D, Dillies, K4, Needle, Candy
Meperidine (Demerol®)	Tablet, liquid	Swallowed, snorted, injected	Demmies, Pain Killer
Methadone (Dolophine®, Methadose®)	Tablet, dispersible tablet, liquid	Swallowed, injected	Adimone, Biscuits, Fizzies, Jungle Juice, Maria, Wafer *With MDMA:* Chocolate Chip Cookies
Morphine *(Duramorph®, MS Contin®)*	Tablet, liquid, capsule, suppository	Injected, swallowed, smoked	Dreamer, First Line, Joy Juice, Morpho, Miss Emma, Monkey, White Snuff, Mister Blue, Unkie
Oxycodone (OxyContin®, Percodan®, Percocet®, and others)	Capsule, liquid, tablet	Swallowed, snorted, injected	30s, 40s, 512s, Oxy, Beans, Blues, Buttons, Cotton, Kickers, Killers, Percs, Roxy
Oxymorphone (Opana®)	Tablet	Swallowed, snorted, injected	Biscuits, Blue Heaven, Blues, Mrs. O, O Bomb, Octagons, Stop Signs

Table 1. Nine different classifications of prescription opioids according to the NIH. Includes the commercial names, common forms, common ways each type of prescription opioids are taken, and common street names. The common form taken pertains to the misuse of prescription opioids.[16]

Appropriate prescription and use of opioids

Three important factors should be considered when medical professions are deciding whether or not to prescribe opioids to a patient for their pain: the severity of the pain, the type of pain, and the duration of the pain.[6] Opioids should be reserved only for severe pain. A common example of the unnecessary prescription of opioid is when dentist and oral surgeon prescribe patients up to a week's worth of opioids when removing their wisdom teeth, despite the fact that most people can manage the pain using Motrin, Ibuprofen, or Tylenol.[6] Opioids are commonly prescribed to treat the intense pain stemming from cancer. Opioids have proven to be less effective on patients experiencing neuropathic pain.[6] Much of the research concerning opioid duration has shown that opioids are most effective for short-term pain, while there is very little evidence suggesting that opioids are an effective long-term treatment for chronic pain. Medical professionals define chronic pain as pain that lasts three or more months.[6] There has been a debate as to whether opioids should be used for chronic, non-cancer pain. Most medical professionals think that a prescription for opioids should rarely be given to someone with chronic, non-cancer pain because chronic pain is usually a product of a nervous system that has veered from its normal function. Chronic pain is now considered a disease due to its impact on peoples' lives and ability to function as well as its underlying mechanisms.[6] Many medical professionals also consider the possibility of opioid dependence or addiction when prescribing opioids, especially to those who are uneducated about their severe addictive qualities.

A statewide retrospective cohort study was done on residents in Oregon to determine the association between initial opioid prescribing patterns and subsequent long-term use among opioid-naïve patients.[18] Researchers examined prescriptions linked to death certificates and hospital discharges, observing patients that filled opioid prescription during a year-long period with no opioid prescription fillings that previous year.[18] They defined a long-term user as a patient with six or more opioid prescription fills during the duration of a year. There were 536,767 opioid naïve patients that filled an opioid prescription. 5% of those patients, or 26,785 people, became long-term users. It was concluded from the results of the study that, "Patients initiating with long-acting opioids had a higher risk of long-term use than those initiating with short-acting drugs. Early opioid prescribing patterns are associated with long-term use…clinicians have greater control over initial prescribing."[18] The results of this study not only show how opioids should only be prescribed for short-term use, but also how important it is for healthcare providers to educate patients when prescribing them opioids.

A nationwide study conducted from 2015-2017 sought to determine whether the adoption of laws that limit opioid prescribing or dispensing was associated with the amount or volume of opioids that were being distributed in the states.[19] The information used in the study was obtained from the U.S. Drug Enforcement Administration. The controls were states that did not have opioid prescribing laws from 2015-2017. The study was concluded that there was not an association between adoption of opioid prescribing laws and the number of opioids distributed.[19]

Fentanyl

Fentanyl (Figure 7) is a synthetic opioid, which is a mu-opioid agonist that binds to opioid receptors and leads to respiratory and central nervous system depression.[20] It has a stronger affinity for opioid receptors, which is why greater doses of naloxone, an opioid overdose reversal drug, are required to combat the effects of Fentanyl.[20] Fentanyl is 100 times more potent than Morphine, which led it to be approved by the FDA and incorporated into anesthesia practice in the United States.[21] It was finally approved for clinical use in 1972.[20] Fentanyl generated 50 million dollars per year for the first three to five years that it was available in the United States.[21] But it still remained widely unknown outside of the operating room, but 30 years later Fentanyl started to receive widespread popularity. It became popular in the operating room because of the cardiovascular stability that was observed in surgeries where fentanyl was administered to the patients.[21]

The presence of Fentanyl can be detected using GC-MS (gas chromatography mass spectrometry) and LC-MS (liquid chromatography tandem mass spectrometry).[20] The illicit manufacturing of Fentanyl is responsible for the rapid increase in the number of opioid-related overdoses and deaths, but fentanyl analogs including Acetylfentanyl, Furanylfentanyl, and Carefentanil have also contributed.[22] Carfentanil is estimated to be almost 10,000 times more potent than Morphine. Even though Fentanyl analogs are similar in structure to fFentanyl, they commonly go undetected because specialized toxicology testing is required.

A study was done to explore the effects of Fentanyl on antinociceptin and respiratory depression in order to integrate the risk and benefit into a single function.[23]

The important information obtained from this study was how to find the threshold at which the probability of respiratory depression exceeds that of analgesia, which is the inability to feel pain. Due to the great potency, this threshold for each person is extremely specific.

CHAPTER THREE

Opioid Misuse, Addiction, and Overdose

Opioid Tolerance

After taking opioids for a few days, a patient or person may need to take a greater number of opioids in order to achieve the pain-relieving effect. It could be said that this person is starting to develop an opioid tolerance. Opioid tolerance can be best described at the molecular level. There are opioid receptors on the surface of cells that become desensitized to the opioids being put into the body; consequently, the cell starts to produce fewer opioid receptors.[6] Opioid tolerance is one of a couple attributes of opioids that causes them to have a high risk of overdose. If someone that has been taking opioids stops, it only takes a few days for their body to revert back to its original state; that is, their body's state before taking opioids. If this same person decides to start taking opioids again, a small number of opioids will have a great effect. The problem lies in the fact that most people go back to taking the same number of opioids as when they stopped, often resulting in an overdose since their body no longer has a tolerance to opioids.

Opioid Withdrawal

Opioid withdrawal is a set of symptoms experienced by someone who has been taking at least 60 mg of Morphine or a Morphine-equivalent for more than a week, before abruptly stopping or being cut off.[6] According to NIH, common withdrawal symptoms from opioids are restlessness, muscle and bone pain, insomnia, diarrhea, vomiting, cold

flashes with goose bumps, and leg movements.[11] Due to the fact that opioid responses differ from person to person, the withdrawal symptoms and severity felt also differs. There are thought to be two main phases of opioid withdrawal. First, the initial phase, which is the most severe and is accompanied by symptoms similar to that of a bad case of the flu. Second, the protracted phase, is accompanied by restlessness, insomnia, and fatigue felt after the initial phase symptoms have passed.[6] Although opioid withdrawal itself is not considered fatal, people have died from dehydration when they experienced nausea, diarrhea, and vomiting associated with opioid withdrawal. The onset, severity, and duration of someone's opioid withdrawal depends on the following factors: type of opioid, dose, method of use, and length of time the opioid was used.[6]

Physical Dependence on Opioids

Physical dependence on opioids, opioid tolerance, and opioid withdrawal are closely related concepts. According to Dr. Yngvild Olsen and Dr. Joshua Sharfstein, an accurate statement a patient or person might say to describe their opioid habit that connects physical dependence, tolerance, and withdrawal would be as follows, "My body has become tolerant to opioids, and if I stopped using abruptly, I would experience withdrawal. That means I am now physically dependent."[6] A key point to make about physical dependence on opioids is that it is a result of biology alone. Anyone who takes 60 mg or more of Morphine or a Morphine-equivalent for a week or longer will develop a physical dependence on opioids regardless of whether they are injecting heroin or taking Oxycodone for chronic pain.[6] In summary, the development of a physical dependence on opioids does not encompass counterproductive behaviors. This is one of the distinctions that makes physical dependence and addiction two different concepts.[6] Addiction

involves counterproductive behaviors, while physical dependence is a product of biology and how the human body functions and responds to environmental factors. Not everyone who uses opioids to treat pain will develop an addiction to them. It is common for people to develop a physical dependence on opioids without becoming addicted to them.

Opioid Misuse

Opioid misuse occurs anytime a person takes opioids without a legitimate medical reason. The main risk associated with misusing prescription opioids is that pharmaceutical companies produce these medications to be taken in specific amounts, so overdosing is more likely to occur. A risk with misusing opioids purchased on the street, such as heroin, is that it is frequently cut with harmful material, like talcum powder. However, the greatest risk with misusing street opioids like heroin is that a lot of times it is mixed with fentanyl, which greatly increases the chance of overdose.[6]

Opioid Addiction

According to Dr. Yngvild Olsen and Dr. Joshua Sharfstein, addiction can be characterized by "pathological craving and compulsion that drives someone to keep using a substance even in the face of severe negative consequences to the person's life, including the threat of death."[6] In regards to treating addiction like a disease, one has to remember that addiction reflects "a dysfunction in the brain circuits involved in reward, learning, memory, and motivation."[6] The effects felt by someone addicted to opioids can be explained best at the molecular level. Many scientists classify addiction as a brain disease because functional changes take place as well as the overall disruption of circuits in the brain that are involved in pleasure, motivation impulse control, stress response,

judgement, and even self-awareness.[6] Opioid addiction can be classified as a chronic illness because of two reasons: (1) there is no cure, and (2) relapse is always a possibility. The clinical term for opioid addiction is, 'opioid use disorder'.[6]

An important question to answer raised when discussing addiction is: why do some people get addicted to opioids and other do not? There are three main factors that need to be considered when trying to understand why a patient or person has developed an opioid addiction: individual factors, the environment, and the opioids themselves.[6] Individual factors include genetics, and there are genes that are related to opioid receptors and reward pathways that are not fully understood yet. 30% of people who are given a single dose of Morphine or Codeine end up experiencing nausea, making them less likely to develop an addiction to opioids. In relation to the environment surrounding someone who might become addicted to opioids, the greater the availability or access to opioids, the greater the risk of addiction. If an opioid has a high potency and can get to the brain quickly then the sense of euphoria felt is greater.[24]

Opioid Addiction & Tolerance on the Molecular Level

Behaviors associated with opioid addiction can be explained by what occurs on a molecular level in the human body. Opioid medications mimic natural endorphins by binding to opioid receptors in the CNS and PNS with variable specificity.[25] They are able to do this because both endogenous opioids (endorphins) and exogenous opioids (opioid medications) share a beta-phenylethylamine group (**Figure 8**), which is the moiety that binds to the opioid receptor. Additionally, "acute administration of exogenous opioids inhibits the productions of endogenous opiates. Patients undergoing general anesthesia have shown as significant increase in beta-endorphins during surgery."[25] This is an

important piece of information because it helps researchers to understand why the chronic administration of exogenous opioids inhibits the production of endogenous opioids and opioid receptors. This occurs because a decrease in endorphin production leads to a down regulation of the POMC gene, which is responsible for encoding opioid receptors.[25] Another factor that contributes to both tolerance and addiction to opioids are peptides called anti-opioid peptides. Anti-opioid peptides bind to opioid receptors, which causes a decreased affinity of those opioid receptors for endorphins and similar opioids. The down regulation of opioid receptors and endorphins, as well as the production of anti-opioid peptides occurs over a period of time, and throughout that period of time, the patient or person consuming the opioids will require an increasing amount of opioids in order to achieve the same level of analgesia. This phenomenon has been described previously as tolerance.[25]

Addiction to opioids then incorporates the dopaminergic reward system. "Opioids in the CNS exert their analgesic effect by increasing dopamine release by disinhibiting GABA's effect on dopaminergic neurons."[25] These dopaminergic neurons are associated with the reward center of the brain. In order for patients who have developed a tolerance to opioids to maintain a normal level of dopamine, they have to consume an increasing amount of exogenous opioids. When they do not receive an ample amount of exogenous opioids in order to maintain dopamine homeostasis, they experience severe withdrawal symptoms.[25]

Opioid Overdose

Consuming too many opioids results in an overdose because it suppresses breathing. When someone has suppressed breathing and therefore is not receiving sufficient oxygen, after five minutes their brain cells start to die, and their heart slows.[6] This results in the build-up of carbon dioxide and other toxins in the body, which proceed to poison all the other organs in the body. It only takes minutes after an opioid overdose to cause irreversible damage to the body.[6] The following factors impact the risk of opioid overdose: type of opioid, amount, potency, medical conditions, and other substances present in the medication taken or in the body at the time the opioid was consumed.[6]

CHAPTER FOUR

Opioid Receptors and Cell Signaling Pathways

Opioid Receptors & Their Corresponding Ligands

Opioid receptors are part of the seven transmembrane-spanning (7TM) G-protein-coupled receptors (GCPRs) superfamily (Figure 9). A G Protein-Coupled Receptors bind to extracellular substances and transmit signals from these extracellular substances to an intracellular molecule known as a G-protein.[26] GPCRs bind to opioids or neurotransmitters outside the cell, and then set in motion a response through G-protein inside the cell. In general, GCPRs play a significant role in mediating the actions of neurotransmitters and hormones.[27] Opioid receptors are a peculiar group in this superfamily because they can be activated endogenously and exogenously. Opioid receptors are activated endogenously by opioid peptides that are produced inside the body. They are activated exogenously by the administration of opioid compounds.[27] There are three major opioid receptor families: mu-opioid receptor (MOR) (Figure 10), the kappa-opioid receptor (KOR) (Figure 11), and delta-opioid receptor (DOR) (Figure 12).[28] Another opioid receptor family that was discovered later on is Nociceptin Opioid Receptor (NOR). Nocicpetin, as a ligand, has a 1000-fold higher affinity for NOR (Figure 13) than KOR.[29] These receptors are involved not only in pain modulation and addiction, but also in regulation of membrane ionic homeostasis, cell proliferation, emotional response, epileptic seizures, immune function, feeding, obesity, respiratory and cardiovascular control, and some neurodegenerative disorders.[28]

Enkephalins and endorphins are small peptide neurotransmitters that are the natural inhibitors of pain signals; and they accomplish this by binding to opioid receptors in pain-signaling cells of the nervous system.[30] Opioids operate in a similar way once administered. When the pain blocking signal requires inhibition, enkephalins and endorphins are broken down by peptide-cutting enzymes. An example of a peptide-cutting enzyme is Dipeptidyl peptidase III (Figure 14), which breaks down enkephalins and endorphins by hydrolyzing C and N terminal residues of peptides. Enkephalins and endorphins are considered endogenous ligands for opioid receptors, and opioids are considered exogenous ligands for opioid receptors. Endogenous opioid ligands can come from the same or different precursor proteins. Table 2 depicts the common endogenous opioids and their corresponding preferred receptors.[28] Mammalian opioid peptides are all derived from the following three precursors: pro-opiomelanocortin (POMC), pro-enkephalin (PENK), and pro-dynorphin (PDYN). Each of these three precursors are translated from different genes.[28] Beta-endorphin (Figure 6) is an exogenous ligand that comes from the isolation of a 31-amino acid sequence of beta-lipotropin. Dynorphins (Figure 15) come from a series of N-terminal Leu sequences that were isolated.

Despite the development of a plethora of exogenous opioids, Morphine continues to be the most popular exogenous opioid for pain relief. It is known as the quintessential MOR agonist, and has a higher affinity for MOR than for DOR or KOR.[28]

Although endogenous opioid peptides do not have a high selectivity or specificity for a particular type of opioid receptor, opioid receptors have a high sequence homology. The only exception to this is endomorphins.[28] Endomorphins are considered to be the natural neurotransmitter central to pain relief. The reasons for this absence of high

selectivity is because of the following: "(1) all the peptide ligands contain the N-terminal residue Tyr (except Phe in the case of nociception), comparable to a functional hydroxyl group in the morphians, which is a requirement for interaction within ligand-bind domain of opioid receptors; (2) MOR, DOR, and KOR have many common structural similarities in their primary structures, in addition to function and intracellular signaling mechanisms; and (3) the formation of homomeric and heteromeric complexes between opioid receptors and non-opioid receptors modify their response to a given opioid ligand."[28] In regards to the last reason, this just means that an interaction between an opioid with different opioid receptor complexes could lead a similar outcome.[28]

Naloxone: An Opioid Antagonist

Naloxone is a medication that quickly reverses an opioid overdose. Naloxone can be administered in two forms: an injection into the muscle or a nasal spray. Nasal administration of Naloxone requires CPR in order to make sure the Naloxone is absorbed into the blood through the lungs.[6] Regardless of how the naloxone is administered, once it is in the blood stream, it travels to the brain where it blocks opioids from binding to the opioid receptors. Naloxone has a higher selectivity for the opioid receptors, which allows it to outcompete the opioids when binding to the opioid receptors, therefore Naloxone is able to reverse the effects of the opioids.[6] An interesting phenomenon occurs in people who have just overdosed on opioids and then received naloxone to reverse that overdose: they overdose again a few hours later without taking any more opioids. Why does this happen? Once naloxone is administered, either by injection or through nasal spray, it begins to breakdown. If the opioid that caused the overdose persists for longer than naloxone in the body, which is a common characteristic for most opioids, then that person

is at a great risk of overdosing again. This is why it is recommended for people who overdose to seek medical attention until they are fully recovered and everything is out of their system.[6]

Naloxone is a competitive opioid antagonist and a Thebaine derivative. It is used to inhibit the following opioid analgesics: euphoria, sedation, respiratory depression, miosis, bradycardia, and physical dependence.[31] Naloxone has a high affinity for mu-opioid receptors (MORs), but can also bind to kappa-opioid receptors (KORs) and delta-opioid receptors (DORs) with a lesser affinity.[31] It binds specifically to opioid receptors in the central nervous system. The main reason why Naloxone is administered to an individual or patient suffering from an opioid overdose is that is reverses respiratory depression, which is usually the cause of death associated with opioid overdosage.[31] According to PubChem, "Naloxone is a synthetic Morphinane alkaloid that is Morphinone in which the enone double bond has been reduced to a single bond, the hydrogen at position 14 has been replaced by a hydroxy group, and the methyl group attached to nitrogen has been replaced by an allyl group."[31] A visual comparison of Naloxone with Morphine, as described above, can be done by comparing **Figure 16** and Figure 5.

Endogenous Ligands	Selectivity
Endorphins	MOR
Enkephalins	DOR
Dynorphins	KOR
Nociceptin	NOR
Endomorphins	MOR
Morphiceptin	MOR

Table 2. Common Endogenous Opioids and their Preferred Receptors.[28]

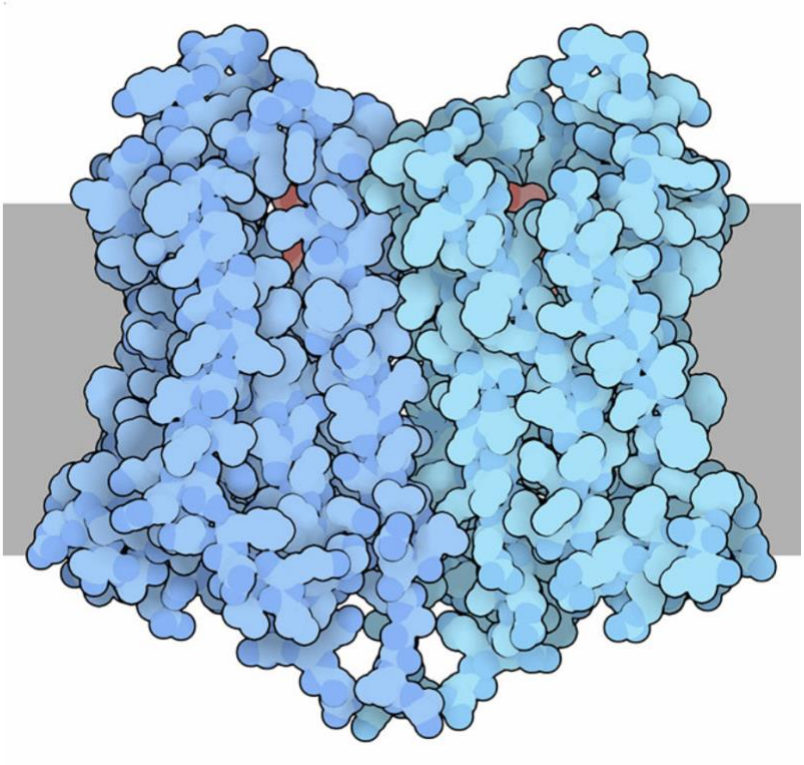

Figure 9. Transmembrane opioid receptor depicted in blue. The cell membrane is depicted in grey, and a morphine analog is depicted in red.[30]

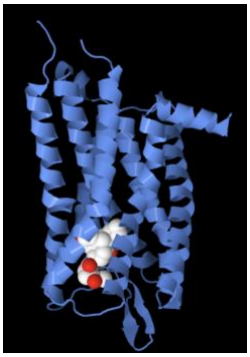

Figure 10. 3D depiction of a mu-opioid receptor (MOR). Drugs and inhibitors bind in the neurotransmitter site and are depicted in red. Composed of a barrel and seven alpha-helices.[30]

Figure 11. 3D depiction of a kappa-opioid receptor (KOR). Drugs and inhibitors bind in the neurotransmitter site and are depicted in red. Composed of a barrel and seven alpha-helices.[30]

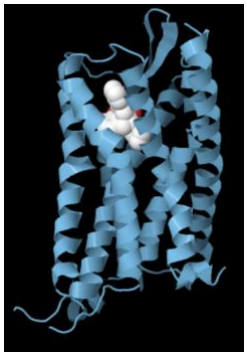

Figure 12. 3D depiction of a delta-opioid receptor (KOR). Drugs and inhibitors bind in the neurotransmitter site and are depicted in red. Composed of a barrel and seven alpha-helices.[30]

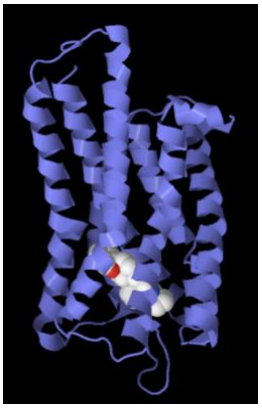

Figure 13. 3D depiction of NOR. Drugs and inhibitors bind in the neurotransmitter site and are depicted in red. Composed of a barrel and seven alpha-helices.[30]

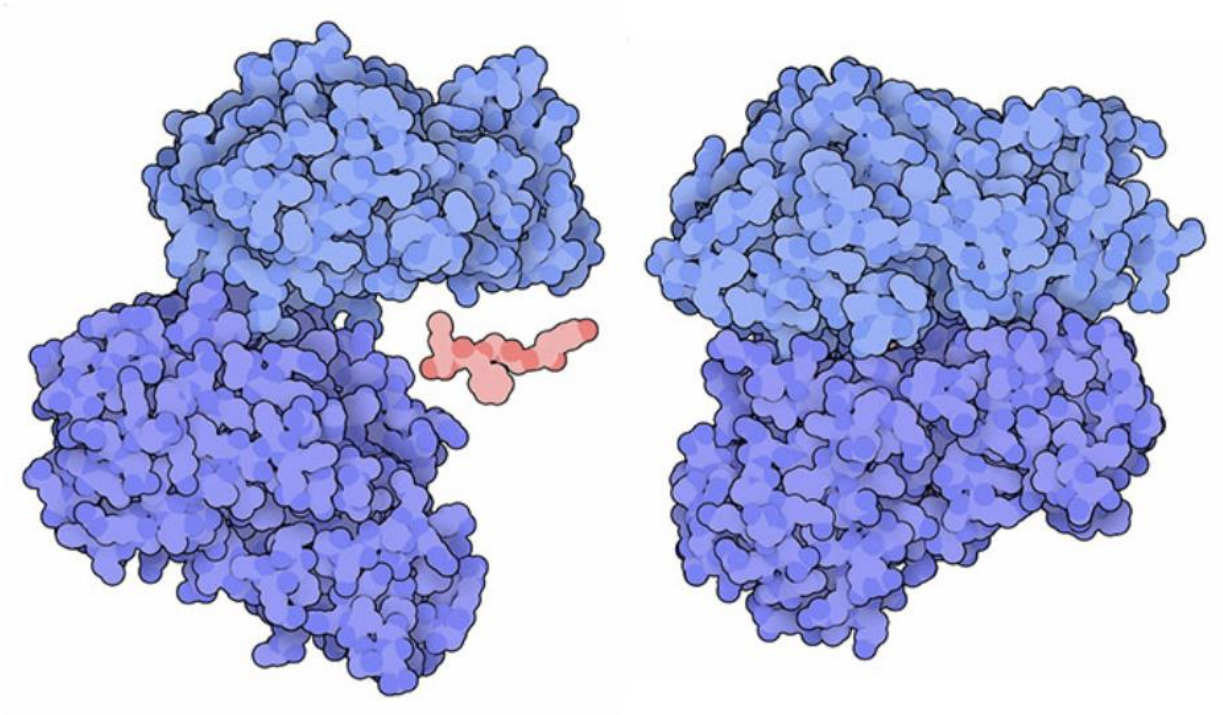

Figure 14. Open (right) and closed (left) forms of dipeptidyl peptidase III. Enkephalin depicted in red.[30]

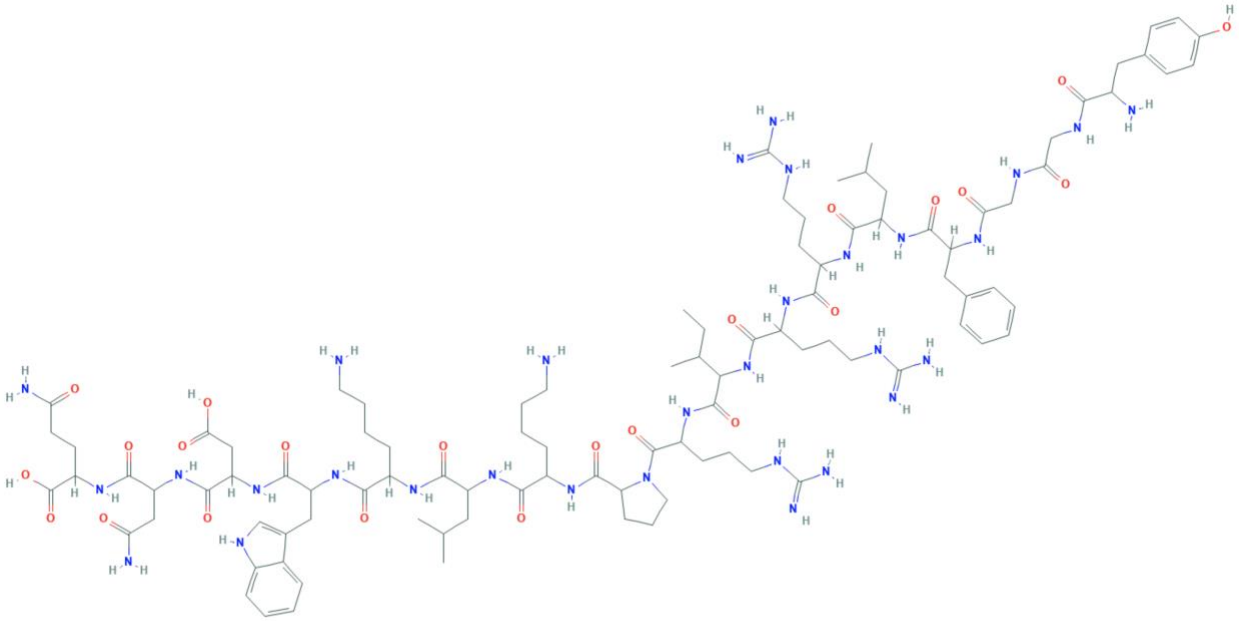

Figure 15. Chemical structure of dynorphin, an endogenous ligand for opioid receptors.[32]

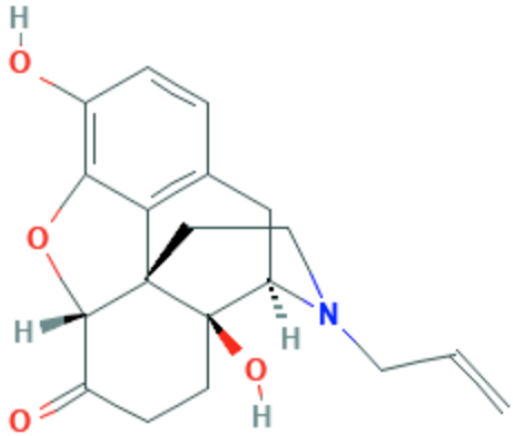

Figure 16. Chemical Structure of Naloxone, an opioid receptor antagonist.

CONCLUSION

Opioid Alternative Research & Chronic Pain Alternative Treatments

Opioid Alternatives

One of the best ways to combat the opioid epidemic would be to find a pain-relieving alternative that possesses little to none of the addictive qualities that opioids do. An important step in synthesizing this opioid alternative is to understand an opioid's mechanism and which steps of that cell signaling pathway contribute to its addictive qualities. Opioids bind to GCPRs, which triggers a signaling cascade that results in the down regulation of pain. However, the opioid has to be protonated in order for it to bind to the GCPR embedded in the cell membrane. This characteristic provides an avenue to explore a nontoxic opioid that is protonated and binds to a GPCR only at the low pH of tissue that is injured or inflamed.[33] Fentanyl is a possible model to research this alternative because it is protonated and binds to the GPCR at a physiological pH and a low pH. Research is currently being conducted on NFEPP, which is a fluorinated Fentanyl derivative.[33] Since the mechanism of how it binds to GCPRs is mostly unknown, researchers are focused on deriving a potential energy function using extensive quantum mechanical and classical computations. The main roadblock to this specific research is that fluorination changes the electronic ground state properties of Fentanyl. This means that the distinct torsional and electrostatic properties of fentanyl and NFEPP affect how each of them binds of GPCRs.[33]

Alternative Treatments for Chronic Pain

A current alternative therapy for chronic pain is 9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The mechanism for CBD is currently unknown, and its side effects have been labeled as benign when being compared to its psychoactive counterpart, THC.[34] Nabiximols are the current pharmaceutical products for the treatment of chronic pain. They contain a set ration of THC mixed with CBD. Nabiximols have shown some evidence for treating chronic pain, while the efficacy of CBD is still not certain.[34]

When misused, opioids can have many negative short-term and long-term effects. Regardless, opioids are considered to be a monumental medical advancement when used appropriately. They are best used for perioperative, and pain associated with terminal cancer. The problems arise when inappropriate prescription of opioids occurs, there is a lack of understanding of the potential adverse effects of long-term use, or the occurrence of opioid misuse, abuse, and dependence. Opioids should not be used for chronic pain because their long-term risks do not outweigh their benefits. This is why researchers are trying to develop a nontoxic opioid alternative, and also why healthcare professionals are looking to alternative treatments for chronic pain like Nabiximols.

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