DISCOVERY: Georgia State Honors College Undergraduate Research Journal

Volume 4 Article 4

2019

Analysis of the Genetic and Neurological Components of Opioid Addiction, with Public Health Perspectives of the Opioid Epidemic in the United States of America

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Cover Page Footnote
Dr. Robert Maxwell

INTRODUCTION

In the United States of America, the use and abuse of opioids has reached epidemic proportions. In 2017, the U.S. Department of Health and Human Services declared the opioid crisis a public health emergency as the rates of overdose deaths continued to rise. The same year as this declaration, more Americans died due to drug overdoses than the number of deaths from HIV/AIDS at the peak of the epidemic in 1995. This epidemic has killed more Americans than the total number of American deaths in the Vietnam War. The primary driver of these overdose deaths is due to opioids, both prescription painkillers such as morphine and oxycodone and illicit drugs such as heroin. This paper looks to analyze the various contributing factors leading to addiction, and the implications on society with such a large population of Americans facing addiction.

NERVOUS SYSTEM INTRODUCTION

The nervous system is divided into the central nervous system (CNS) which contains the brain and spinal cord, and the peripheral nervous system (PNS) which includes the nerves that travel throughout the body. Drug abuse impacts the CNS and many functions involved in heart rate, sleeping, and breathing through the brain stem; emotions, including happiness through the limbic system; and decision-making abilities through the cerebral cortex. The different parts of the human brain can communicate with each other via neurons and neurotransmitters. Neurons are brain cells used to relay signals, and neurotransmitters are the chemical messengers that are the signals. Each neuron has different receptors, which allow for the binding of a specific neurotransmitter; once bound, an action potential can occur which is the propagation of the signal down the neuron. There are many different types of neurotransmitters but all fall into two

categories: excitatory or inhibitory. Excitatory neurotransmitters will increase the likelihood of a response while inhibitory neurotransmitters do the opposite.

Opioid Neurotransmitters

There are four main classes of opioids: natural opiates, semi-synthetic opiates, fully synthetic opiates, and endogenous opiates. Synthetic and semi-synthetic opioids can interfere with the typical neural pathways involved in sending, receiving, and processing information that allows the different areas of the brain to communicate with each other. The naturally produced endogenous opioids are created in the brain and work to block pain. The opioid epidemic is focused around exogenous opioids, which are chemical signals that are not naturally made by the human body and are instead often prescribed by a healthcare provider. Exogenous opioids are similar in structure to endogenous opioids, and therefore can activate receptors in the brain resulting in the same effects as endogenous opioids. Exogenous opioids can alter certain essential areas of the brain, such as the brain stem, cerebral cortex, and the limbic system (NIDA, 2014).

Pain Sensation

One form of communication between neurons involves pain sensation, and many of the pain pathways utilize opioid neurotransmitters. Neurons sense injuries that occur to the skin and muscles and then signal other neurons in the central nervous system. Pain nerves in the body begin to fire less intensely once natural opioids such as endorphins and enkephalins bind to receptors. However, in instances when there is chronic pain, pain signals are constant. Natural endorphins are not sufficient to deal with this long-lasting chronic pain, and often prescription opioids are prescribed (Akpan & Griffin, 2017).

Opioids, both endogenous and exogenous, affect neural pathways that are involved in pain and pleasure perception; these pathways include the dopaminergic and GABA-nergic

pathways. Opioids can hijack the normal functioning of the reward pathway and activate neurons because the chemical structure resembles that of a natural neurotransmitter. Dopamine is an excitatory neurotransmitter that is present in the mesolimbic dopamine pathway of the brain and regulates feelings of pleasure and emotion (NIDA, 2014). Opioids function to overstimulate neural systems and flood the reward system of the brain with dopamine, releasing 2-10 times the amount of dopamine than what is released on a regular basis (Di Chiara & Imperato, 1988). There are two main ways that the brain works to return to homeostatic levels of dopamine - there will be an overall decreased production of dopamine, or there will be an overall decreased production of the number of dopamine receptors. Abuse of exogenous opioids can lead to a down-regulation of dopamine receptors. This decrease in dopamine signaling leads to those who have been taking opioids being unable to experience even daily pleasures (NIDA, 2014).

While increasing levels of dopamine, opioids also work to relieve pain in the body by suppressing GABA neurotransmission (Basbaum & Fields, 1984). GABA is an inhibitory neurotransmitter found throughout the brain and spinal cord that is primarily involved in controlling thinking and perceiving. By decreasing the functionality of the inhibitory neurotransmitter and increasing the excitatory neurotransmitter, opiates increase feelings of pleasure to such intensity that once an individual stops taking the drug, feelings of intense withdrawal occur. In normal body functioning, when dopamine levels increase, GABA levels tend to increase as well to bring the body back to a homeostatic balance. Opiates, including heroin and morphine, function as agonists at the opioid receptors and activate dopamine in the ventral tegmental area by inhibiting GABAergic neurons (Johnson & North, 1992). Overall, this disinhibition leads to an increase in dopamine neurotransmission and a decrease in GABA neurotransmission, which amplifies the signal elicited by dopamine.

The need to elicit increased dopamine levels forms the basis for the transition from normal reward impulses to addiction. With the consistently elevated levels of dopamine that are present with increased intake of drugs, the level of dopamine receptors decreases, and the levels of presynaptic dopamine transporters also decrease as a compensatory mechanism (Volkow et al., 1993). When opioid drugs are administered repeatedly, the ability of neuronal cells to produce endogenous opioids is inhibited, which is part of the reason that withdrawal symptoms occur with such extreme discomfort (NIDA, 2014).

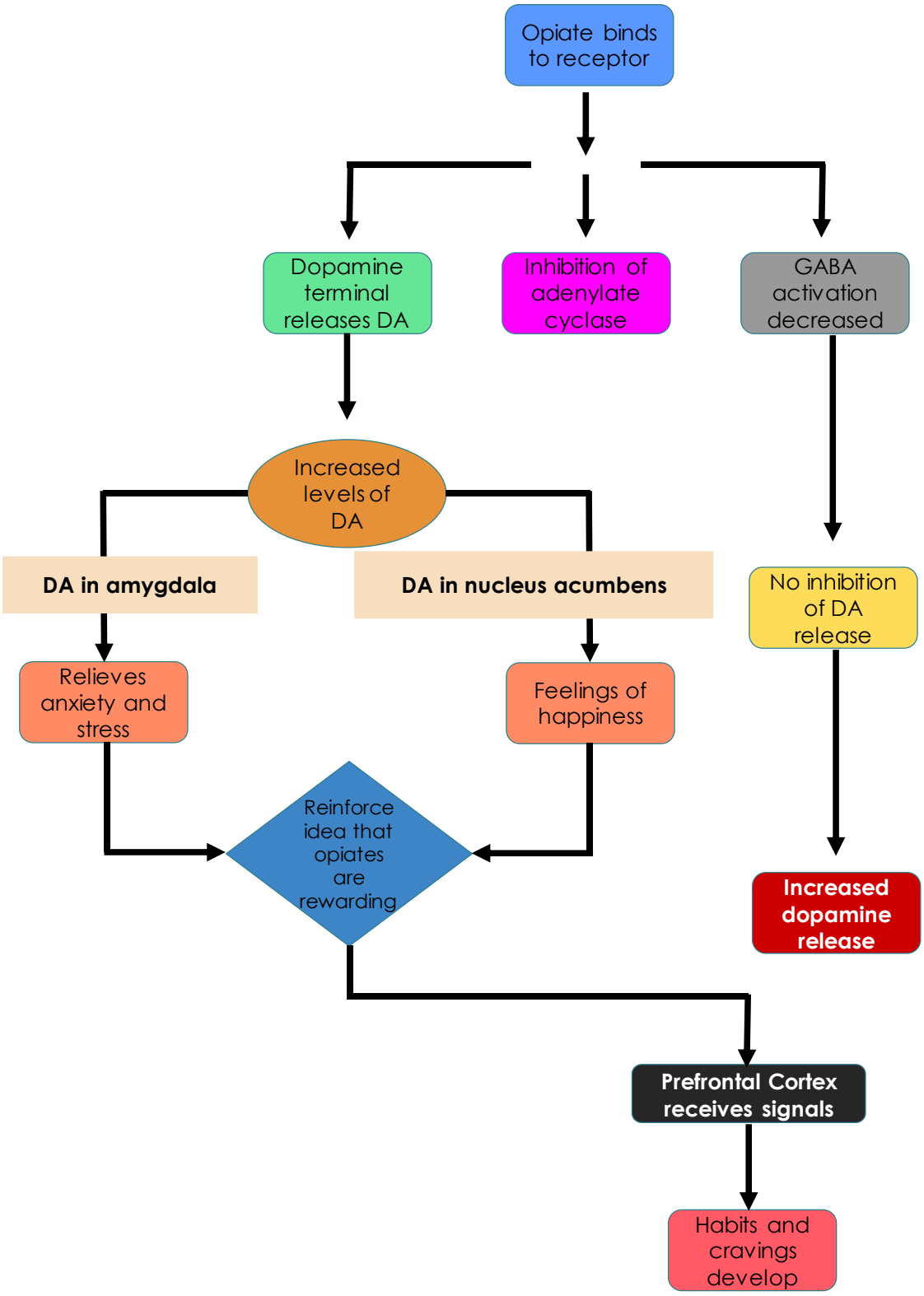

Figure 1: *Pathway for Opioid Dependence*

MOLECULAR MECHANISMS OF OPIOID TOLERANCE

The inhibition of the neural cells to produce these endogenous opioids also leads to opioid tolerance. Tolerance is when the effect of a drug is no longer as strong as it was when first taken, leading to higher doses required to induce a similar effect (NIDA, 2014). Substance addiction occurs when there has been substance abuse at such a repetitive level that the normal circuitry of reward and behaviors is corrupt (Di Chiara & Imperato, 1988).

Once there are excess exogenous opiates in the nervous system, the neurons begin to adapt. The neurons that normally secrete GABA following opioid exposure now begin to produce three to four times more cyclic AMP. Cyclic AMP is part of a second messenger system and functions in intracellular signaling, allowing the neuron to reach threshold potential. Once there is excess cAMP, there is excess neural firing. This adaptation of increased cAMP production will continue even when there are no opioids present, and lead to excess GABA neurotransmitter signaling in the brain (Akpan, N., & Griffin, J. 2017).

Calcium also plays a role in the development of opioid tolerance. When there is an acute administration of opioid agonists, there is a reduction in the calcium content in synaptic vesicles. Since calcium is required for an action potential to begin, the reduced calcium intake caused by opioids will indirectly cause an increase in potassium exiting the cell, leading to a shortening of the repolarization period and a shortening of the action potential duration. (Chahl, 1996). There is a correlation between the ineffective regulation of cAMP caused by opioids and the tolerance induced at a molecular level to opioids. When there are chronic levels of morphine exposure, there is the potential for the upregulation of adenylyl cyclase and protein kinase A (PKA) because opioid receptors couple to adenylate cyclase, which can lead to an inhibition of neurotransmitter release as depicted in Figure 2 (Dang & Christie, 2012).

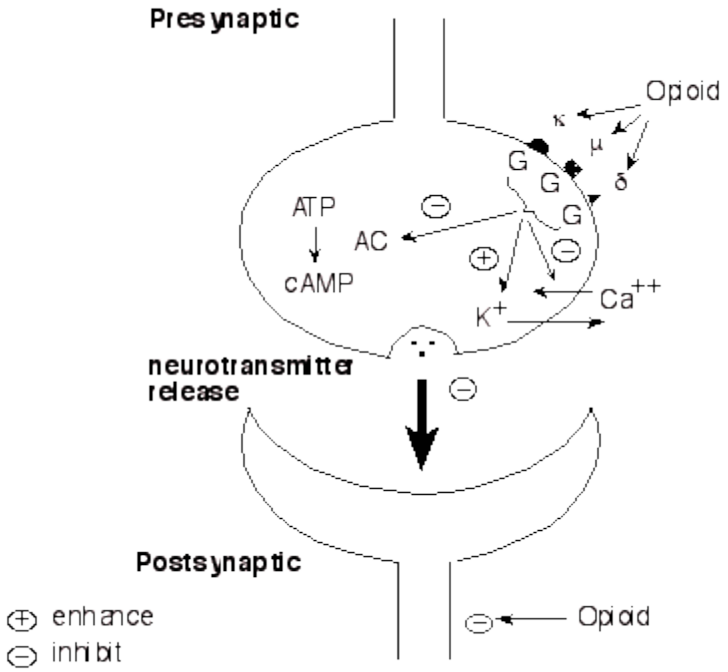

Figure 2: *Mechanism of Opioid Neurotransmitter Release*

This image depicts the proposed impact opioids have on neurons. By inhibiting calcium entry and enhancing potassium exiting, there is an inhibition of neurotransmitter release. Another mechanism is the inhibition of adenylate cyclase to have decreased levels of cAMP (Chahl, 1996).

DOPAMINE REWARD PATHWAY

In 1954, Olds and Milner conducted experiments that established the foundational understanding of reward mechanisms in the brain. The researchers gave rodents the option to repeatedly administer electrical stimulation to the brain. The regions that elicited "pleasure," such as the nucleus accumbens and the septum, would result in continual voluntary stimulation by the mice themselves. The major pathway identified in this reward system was the mesolimbic pathway, also known as the dopamine reward pathway.

The mesolimbic pathway (Figure 3) originates from a group of neurons in the ventral tegmental, area (VTA) and terminates in either the nucleus accumbens of the ventral striatum, the amygdala, bed nucleus of stria terminalis, lateral septal area, or lateral hypothalamus (Gardner & Ashby, 2000). The nucleus accumbens is believed to play an important role with

reward while the amygdala is associated with emotion (S.R.W. Stott, S.-L. Ang, 2013). All rewarding stimuli increase the concentrations of mesolimbic dopamine in the extracellular regions. When drugs activate the neurons in the VTA, there is a release of dopamine into the nucleus accumbens leading to feelings of pleasure (Friedman, D.P. & Rusche S., 1999). Opiates bind to opiate receptors that send a signal to the dopamine terminal to release more dopamine. The activation of opiate receptors leads to a decrease of GABA release, which typically functions to inhibit dopamine (NIDA, 2007). Opiates decrease pain and increase pleasure, which overall leads to a very addictive neurological combination.

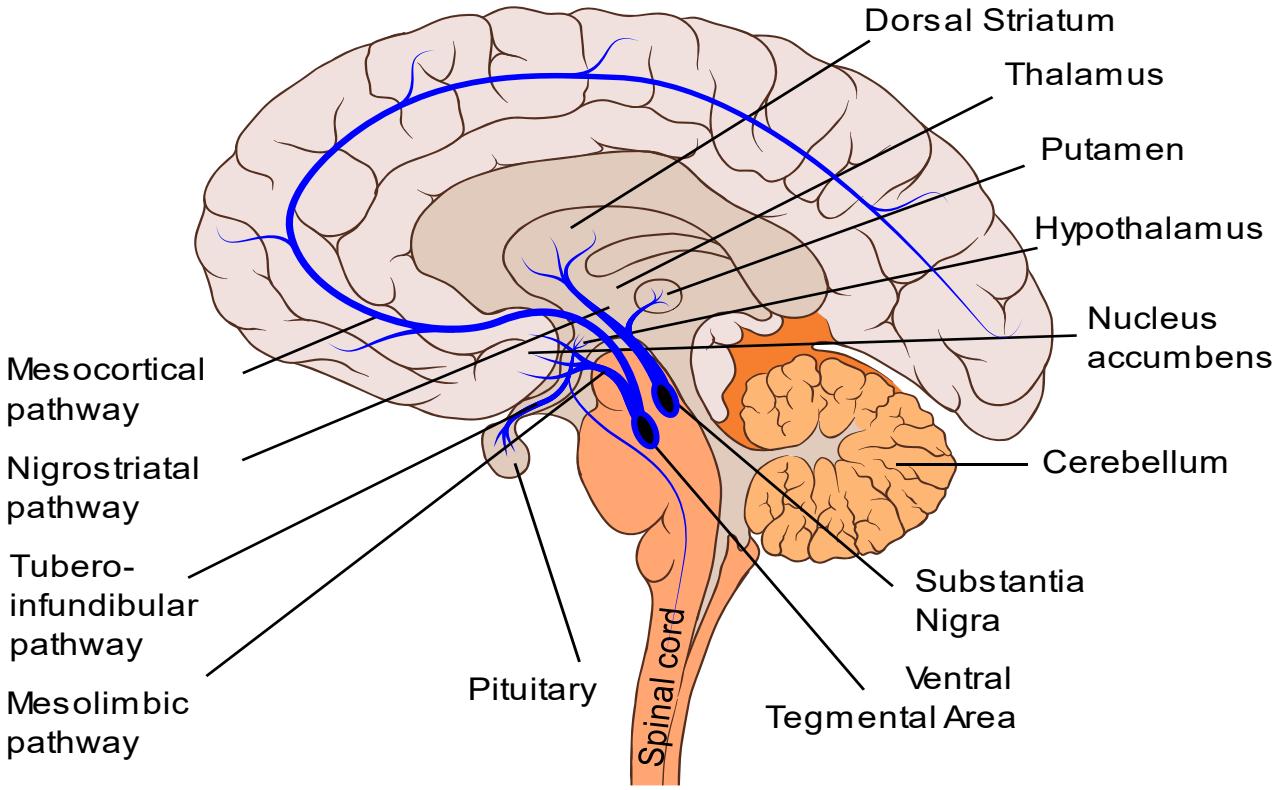

Figure 3: *The Mesolimbic Pathway*
Dopaminergic pathways.svg by Patrick J. Lynch is licensed under CC-BY 3.0.

This pathway is also referred to as the dopaminergic pathway and consists of neurons that have cell bodies that run the entire length of this pathway. These neurons produce dopamine and can send this signal to their destinations.

There are many different effects of dopamine, and the various effects are mediated by five different transmembrane G-protein coupled receptor subtypes. The D1-receptors activate adenylyl cyclase, and the D2-receptors inhibit adenylyl cyclase and activate potassium channels leading to an overall potassium efflux, which causes hyperpolarization in the local potentials in the cell (Missale et al., 1998). The potassium efflux is counteracting the calcium influx, thus reducing the amount of neurotransmitter released.

OPIOID PATHWAY

Opioids function by attaching themselves to opioid receptors present on neurons in the brain, spinal cord, gastrointestinal tract, and other organs in the body. Once the opiate attaches to these receptors, the perception of pain is reduced; however, there are side effects caused by opiates such as drowsiness, respiratory depression, mental confusion, nausea, and constipation due to the widespread presence of opiate receptors in various neural and physiological pathways (Mattoo, 2009).

There are three different types of transmembrane opioid receptors, μ, κ, and δ, to which an opioid can bind. Opioid receptors can be activated by endogenous opioid chemicals such as endorphins and enkephalins or by exogenous chemicals such as prescription opiates (NIDA, 2014). All three receptors are located in pain-modulating pathways within the brain, including the medulla, locus coeruleus, the limbic system, the midbrain, cortical structures, and the periaqueductal gray area (McNicol et al., 2003). Of the three receptors, the μ receptor is primarily responsible for the relative effects of opioids and opiate addiction (Akpan, N., & Griffin, J. 2017).

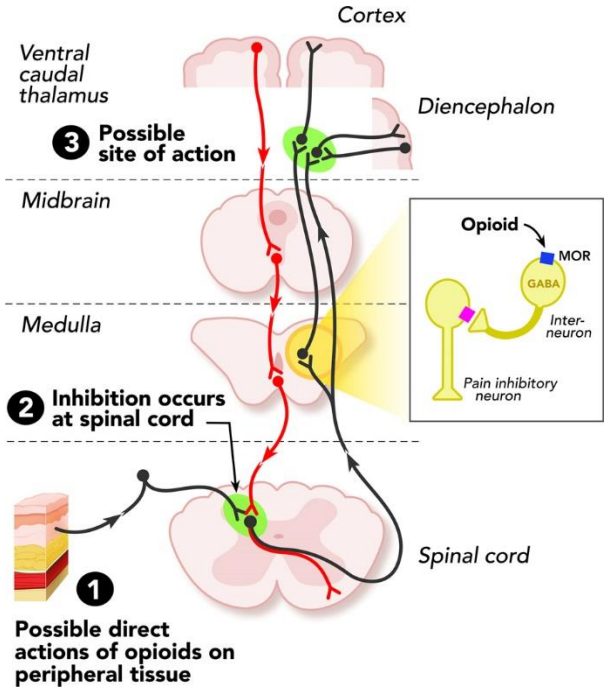

Figure 4: *Site of Action for Opioids*

In this figure, there are two pathways, a gray pathway, which depicts pain transmission from the PNS to the CNS, and a red pathway, which depicts the pain-modulating neurons in the medulla and the mid brain (Al-Hasani & Bruchas, 2011).

Activation of the opioid receptor by an exogenous opioid causes the second messenger system of inhibitory G-protein coupled receptors to be activated. The opioid itself is the first messenger and never enters the cell body, but instead binds to a receptor, which causes a series of activations and inhibitions in the rest of the signaling pathway. The binding of the opioid to the opioid receptor leads to a conformational change in the receptor, activating the coupled G-protein. The Gi receptor is the mechanism most opiates utilize, and this complex leads to a dissociation between the Giα and Giβγ subunits of the G-protein. The Giα molecule inhibits the activation of adenylyl cyclase. Adenylyl cyclase is the enzyme that converts ATP to PPi and cAMP (Childers & Snyder, 1978). The inhibition of adenylyl cyclase leads to a reduction in the cAMP-dependent calcium influx, impacting the polarization of the cell. This disassociation also leads to the interaction of Gα protein with Kir3, which is a rectifying potassium channel. By

deactivating the potassium channel, the cell becomes hyperpolarized, and the neural activity will be dampened (Ippolito, Temkin, Rogalski, & Chavkin, 2002). A similar mechanism occurs for calcium channels, where the disassociated Gβγ subunit directly binds to the channel and reduces the opening of voltage-gated calcium channels (Zamponi & Snutch, 2002). As a result, there is a coupling to potassium channels and a negative modulation for calcium channels for opioid receptors (Al-Hasani & Bruchas, 2011).

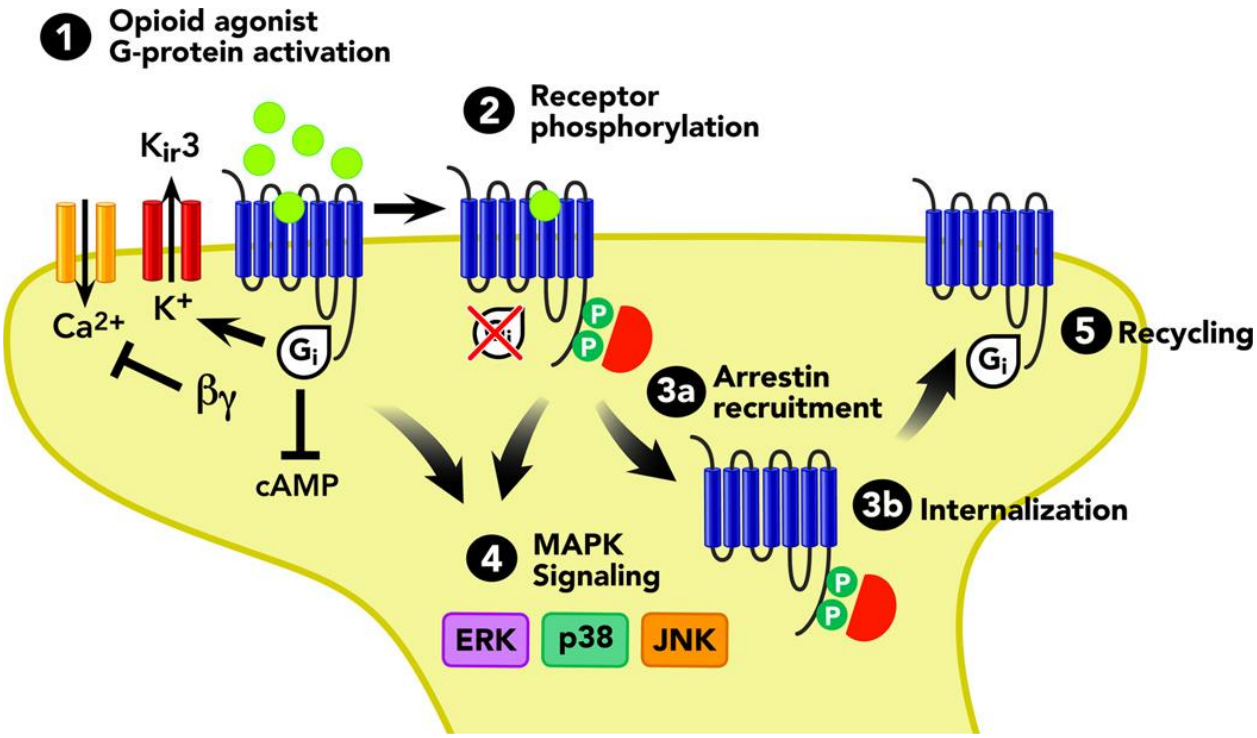

Figure 5: *Opioid Receptor Signaling*

This cartoon depicts the common molecular pathway that opioid receptors use. The arrows refer to activation while the T lines depict inhibition of a signaling molecule. The MAPK signaling molecules that are activated are all kinases that will phosphorylate molecules downstream (Al-Hasani & Bruchas, 2011).

SUMMARY OF BRAIN ANATOMY INVOLVED WITH ADDICTION

The parts of the brain that are involved with the reward pathway are the same as the parts of the brain that are involved with addiction. The release of dopamine in the nucleus accumbens leads the hippocampus to create a conditioned response to the opiate. Along with the hippocampus, the amygdala is typically related to the memory of emotionally arousing events. The hesitation and fear present with new stimuli and the assignment in reward values for existing stimuli is done by this part of the brain. The memories created by these two parts of the brain lead to a conditioned response whenever environmental cues are encountered that remind the individual of their previous drug consumption. (Elliott et al., 2000).

The anterior cingulate is involved with emotional self-control, error detection, and adaptive responses to changing conditions. The anterior cingulate also plays a role in processing conflicts and performance monitoring. The bed nucleus of the stria terminalis (BNST) is located in the extended amygdala and is sensitive to dopamine stimulation. The BNST is involved with the autonomic and behavioral reactions such as the stress response to fearful stimuli. Experiments have shown that this part of the brain is involved in the reinstatement of a drug directly after experiencing a painful stimulus. The dorsolateral prefrontal cortex (DLPFC) is involved with the control and regulation of cognitive activities. The holding/maintaining working memory for the short-term storage is conducted by the DLPFC. The hippocampus is important for acquiring new factual information and forming new memories. Alzheimer's disease and other memory impacting diseases as well as anterograde amnesia are typically the results of damage to the hippocampus. (Elliott et al., 2000).

The orbitofrontal cortex (OFC) is involved when faced with unpredictable situations and is implicated with disorders of impulsivity and decision-making. The medial portion of the OFC

is connected to the hippocampus and cingulate and is involved with assessing the familiarity of a situation to integrate outcome expectancies. The lateral portion of the OFC is connected to the amygdala and is associated with suppressing previously rewarded responses in order to provide terminating signals for changing behavior. The insular cortex is important for processing pain as it receives somatosensory inputs and tends to be activated during acute anxiety. These parts of the brain all work together in the mesolimbic dopamine pathway and can all be impacted by exogenous opiates (Elliott et al., 2000).

GENETICS

While there are many social and economic factors that lead to differences in opioid use disorder between racial groups and genders, there are underlying genetic factors that contribute to this addiction pathway as well (Mistry et al., 2014). Studies of twins consistently demonstrate that familial genetics contribute greatly to addiction (Cadoret, Troughton, & German, 1986). The Harvard Twin Study of Substance Abuse shows that there is a 34% contribution from genetic influences into the variance of abuse (Tsuang et al., 2001). The heritability involved with addiction and drug use behavior is based off multiple genes, and by developing an understanding of these genetic markers, there is the potential to change the way opioid abuse is studied and treated.

The gene that encodes for dopamine receptor D2 (DRD2) is located on chromosome 11q23 and allows for the production of a seven-transmembrane helix receptor that can inhibit adenylyl cyclase through inhibitory G-proteins (Freedman et al., 1994). The allele DRD2 rs1800497 contains a polymorphism that is associated with heroin dependence. The specific polymorphism is at the Taq1 RFLP site rs1800497 and involves a single nucleotide polymorphism (SNP). In a study that compared the allele frequencies in 500 Han Chinese opioid

addicted subjects, the patients who carried at least one copy of this rs1800497 A_1 allele had a mean heroin consumption twice as high as those subjects without this allele (Hou & Li, 2009). This allele is present at a higher frequency in subjects with opioid use disorder and has been associated with successful methadone treatment outcomes (Dalley et al. 2009). In another study involving 95 Caucasian opioid addicted subjects, 19% showed the rs1800497 A_1 allele, compared to the 4.6% occurrence that found in the control subjects with no history of addiction.

There are three different types of G-protein coupled opioid receptors – the μ, κ, and δ receptors (Dalley et al., 2009). The gene that encodes for Opioid Receptor μ 1 (OPRM1) is located on chromosome 6q24-q25 (Kapur et al., 2007). There have been correlations between this gene and many physiological symptoms such as respiratory depression, decreased gastrointestinal motility, and euphoria (Dalley et al., 2009). There are many SNPs present between ethnic variations with opioid abuse and general opioid abuse (Kapur et al., 2007). In an analysis of Hispanic subjects, the SNP occurring at A118G (rs1799971) was significantly higher in those without any opioid dependency. In a study involving Indian subjects, there was a 31% frequency in the A118G SNP gene for those that were opioid dependent (Dond et al., 1998).

Other than the receptors themselves, neurotrophic factors also play a regulatory role in the nervous system. Brain-derived neurotrophic factor (BDNF) is a protein linked to opioid dependence and is encoded by the BDNF gene, which is located on chromosome 11p14 (de Cid et al., 2008). Connecting drug use and drug dependence, this protein is imperative in the reward pathway and regulating cellular signals. Increased concentrations of BDNF in the ventral tegmental area induce over-expression of dopamine receptors leading to a reward state parallel to the type achieved with opioid use (Heidt et al., 2007). In a study with Japanese subjects, an SNP of the gene G196A (rs6265) indicated a link between depression and genotypes. With female

subjects that were homozygous for the G196A allele that encoded for valine, there was a significant increase for reward dependence and extraversion, which negatively correlates to depression. In contrast, subjects that carried the SNP for methionine were more prone to developing depression-related mood disorders. Subjects with the G196A valine allele showed increased levels of BDNF, which leads to increased euphoric events (Itoh et al., 2004).

Introduction to Public Health Concerns

The number of deaths that occurred in the United States from prescription opioids more than quadrupled between 1999-2010 (Volkow et al., 2014). The Council of Economic Advisors estimates that in 2015 the economic cost of the opioid crisis was $504 billion, or 2.8 percent of GDP that year (Council of Economic Advisors, 2017). A majority of these costs are attributed to nonfatal consequences such as healthcare spending, criminal justice costs, fatality costs, and lost productivity due to incarceration and addiction (Florence et al., 2016). The outcomes of increased opioid consumption include sharp increases in emergency room visits for overdose, neonatal abstinence syndrome, and increased mortality (SAMHSA, 2013). With an increase in morbidity and mortality rates due to opioids, it is necessary to utilize a multi-faceted public health approach that employs addiction prevention strategies.

Impact on Heroin Use

The opioid pain relievers (OPR) overdose death rate nearly quadrupled from 1999-2011 (Chen et al., 2014), as shown in Figure 6, and is now cited by the Centers for Disease Control and Prevention (CDC) as the “worst drug overdose epidemic in [US] history” (Paulozzi, 2010). It is important to recognize the relation between OPRs and heroin use. Statistics from the National Survey on Drug Use and Health (NSDUH) indicate 4 out of 5 heroin users began their addiction with OPRs and switched drugs because heroin was cheaper and easier to obtain (Muhuri et al.,

2013). In 2014, national surveillance data showed that 914,000 individuals reported using heroin, which was a 145% increase from seven years prior (Center for Behavioral Health Statistics and Quality, 2014). When looking at the drug overdose crisis holistically, it is necessary to understand the relationship between heroin and opioids to avoid the error of shifting the problem from one drug to another unintentionally.

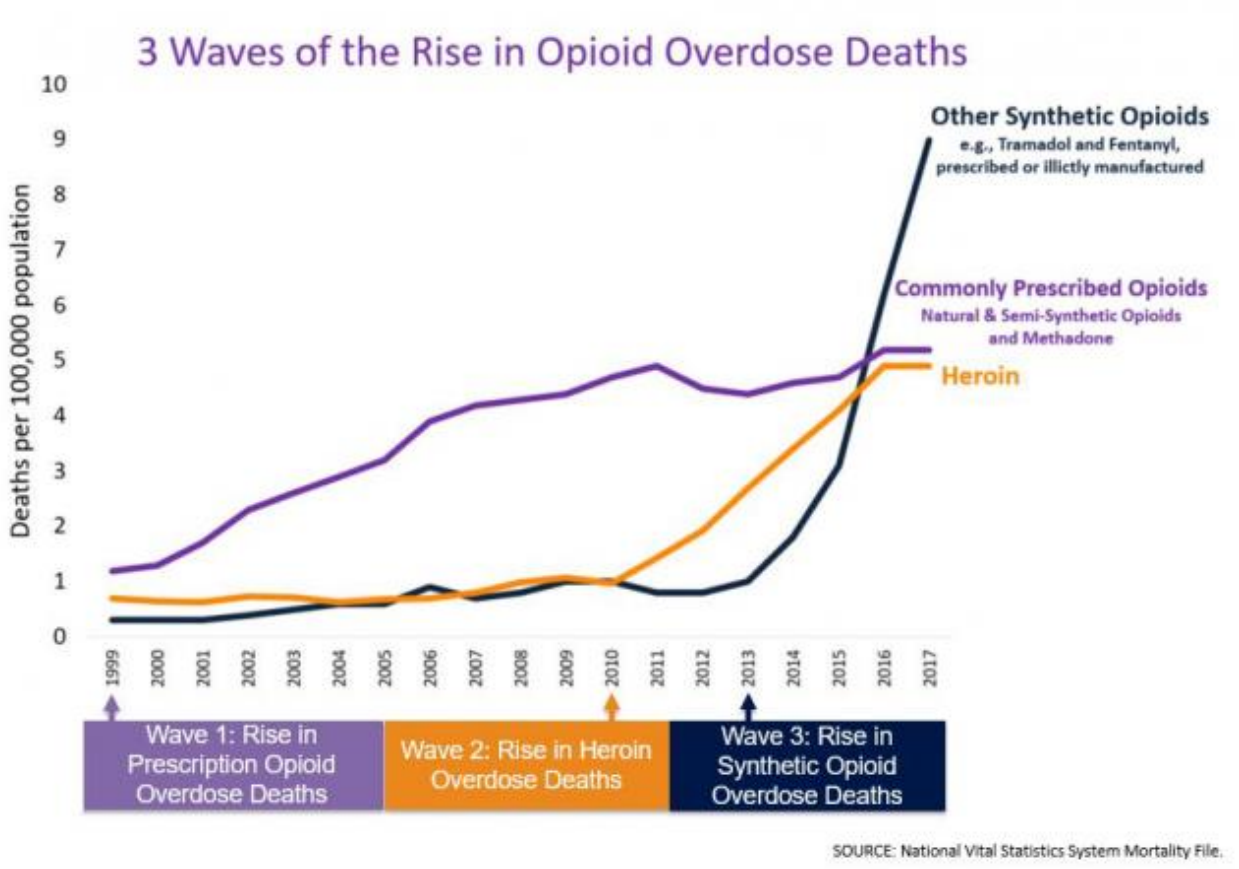

Figure 6: *Three Wave Rise of Opioid Use*

This graph overlays the increases of Heroin, Prescription Opioids, and Other Synthetic Opioids outlined in three distinct waves. The first wave began with the increased prescriptions for opioids which increased until 2010. This was when the prescriptions decreased yet patients remained addicted, many of them switched to heroin which is depicted by the rapid increase in overdose deaths.

HISTORY OF OPIOID ADDICTION IN THE UNITED STATES

In the 1840s, there was an increase in the estimated national supply of opium and morphine imports, which throughout the next 50 years lead to a 538% increase in opioid consumption (Courtwright, 2001). There were many uses for the drug, including the common use of opium by soldiers to treat painful injuries. Physicians at this time often prescribed opiates to their patients as there were few alternatives and the etiology of many chronic and acute diseases were poorly understood. As many advancements in health occurred, the administration of morphine as a primary solution decreased through the means of educated, better-trained health practitioners (Blair, 1919). The rest of the 20th century saw the use of short-lasting, nonmedical opioid increase disproportionately in inner-city, minority populations (DuPont & Greene, 1973).

In 1996, the rate of opioid use began accelerating rapidly due in part to the introduction of OxyContin in 1995 by Purdue Pharma. This drug is an extended-release formula for morphine advertised under the claim that the risk of addiction was minimal to none. Indeed, OxyContin was advertised as appropriate for the treatment of chronic pain. In the seven years that followed the introduction of OxyContin, Purdue Pharma funded over 20,000 educational programs that encouraged the long-term use of OPRs for non-cancer related chronic pain (US GAO). Purdue Pharma financially supported groups such as The Joint Commission, the Federation of State Medical Boards, the American Academy of Pain Medicine, and the American Pain Society – all of whom advocated for the use of OPRs to treat pain (Fauber, 2012). In 2007, the executives of Purdue Pharma pleaded guilty in federal court to criminal charges about misleading health professionals and patients about OxyContin, and they agreed to pay $600 million in fines, one of the largest amounts paid by any drug company. The executives agreed to pay a total of $34.5 million in fines for misbranding, which is a criminal violation (Meier, 2007).

While there have been no long-term quality clinical trials on the efficacy of OPRs for non-cancer chronic pain, there have been surveys of patients indicating that even with opiates they still experience significant chronic pain (Eriksen et al., 2006). The Joint Commission's federally mandated patient satisfaction surveys ask patients to rate how their experience in the hospital was related to pain. This experience relates to the increase in hospital use of OPRs as physicians administer more opiates to have patients provide higher ratings (Herzig et al., 2014).

Overall, the United States has had a complicated relationship with opioid use. In recent history, the rise in opioid overdose death has had three distinct waves, initially in the 1990s with the over-prescription of opioids. The second wave was in 2010 when there was a rapid increase in heroin deaths. The third wave since 2013 includes a rapid increase in overdose deaths due to synthetic opioids such as fentanyl (Centers for Disease Control and Prevention, 2017).

WHO IS USING?

From 2002 to 2012, the use of nonmedical opioids has gradually declined; however, overdose deaths, addiction treatment admissions, and other adverse public health outcomes related to OPRs have increased (SAMHSA (Substance Abuse Ment. Health Serv. Adm.), 2003).

The demographic that abuses non-medically prescribed opioids the most is the young adult population, age 18-25. However, the group with the greatest use of prescription opioids is among adults over the age of 26 (CDC, 2016). From 2013-2014 the rate of opioid overdose deaths for men was three times higher than those of women for populations age 18-34 within the state of Massachusetts (Massachusetts Department of Public Health, 2016).

One study looking at unintentional opioid overdoses in Utah showed that 92% of those who had died from overdose were receiving legitimate opioid prescriptions for their chronic pain. Middle-aged white women aged 55-64 and the elderly visit their physicians with

complaints of pain the most frequently, with rates higher than any other demographic (Blackwell et al., 2014). White women aged 55-64 have experienced the largest increase in accidental opioid overdose deaths over the past decade (CDC, 2013). Death from overdose can occur in non-opioid addicted users, yet it is much more common in individuals who are addicted to opioids.

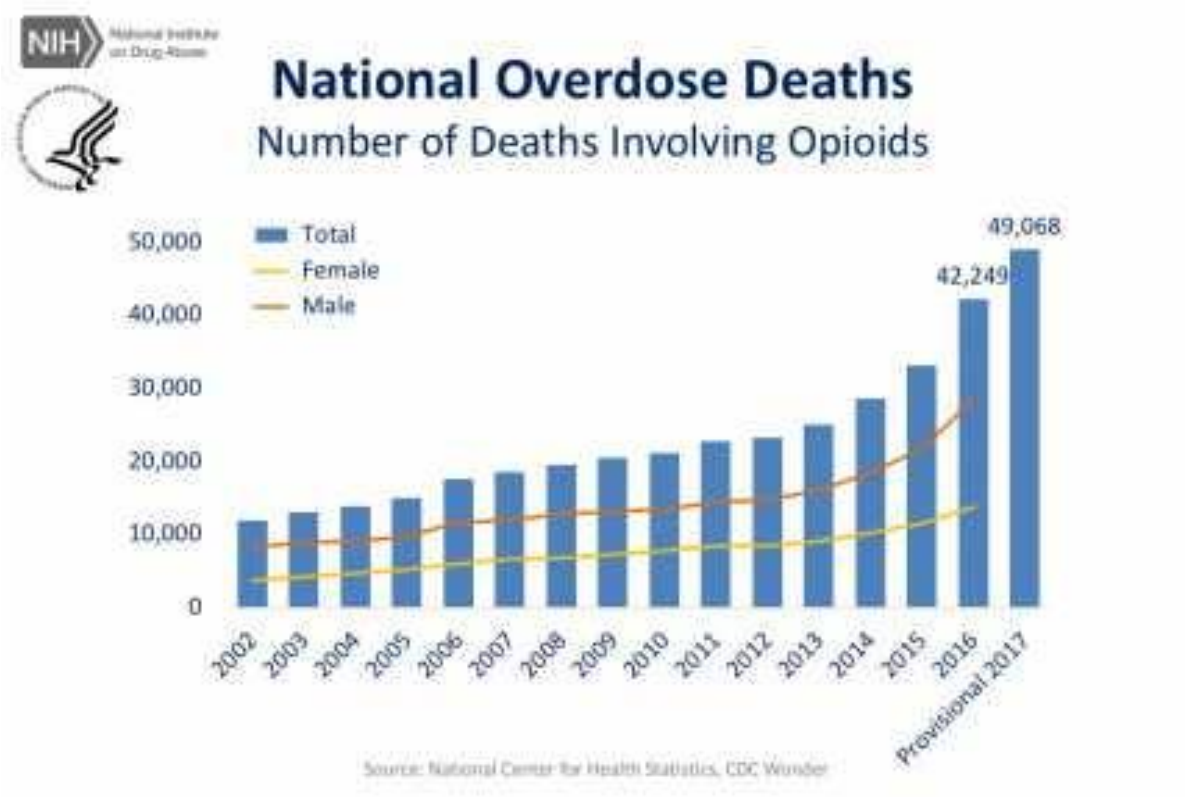

Figure 7: *National Overdose Deaths 2002-Provisional 2017 Involving Opioids*

This bar graph depicts the total number of overdose deaths in the United States that were involving opioid drugs with provisional data from 2017. A line overlay depicting male versus female deaths further divides this graph. There has been a 4.1-fold increase in the total number of deaths involving opioids in the time depicted.

NATIONAL RESPONSE

In October of 2017, the acting Health and Human Services (HHS) Secretary declared the opioid crisis a nationwide public health emergency. In April of the same year, the HHS presented a new

five-point Opioid Strategy. The priorities include: (1) improving access to prevention, treatment, and recovery support services; (2) targeting the availability and distribution of overdose-reversing drugs; (3) strengthening public health data and collection; (4) supporting cutting-edge research on addiction and pain; and (5) advancing the practice of pain management (U.S. Department of Health and Human Services, 2018).

To improve access to treatment and recovery support services, the HHS submitted letters to the governors in every U.S. state offering $485 million in grant money in return for evidence-based treatment and prevention activities. These grants from the Substance Abuse and Mental Health Services Administration complemented grants from the Comprehensive Addiction and Recovery Act (CARA). By providing the funds for a wide range of programs – training for health professionals, prevention programs, technological support, and monitoring programs – there is a focus on recognizing that individual states will tackle their state-wide crises at a level that is specific for their communities (Secretary for Health and Human Services, 2018). Many states have given importance to opioid overdose reversal drugs such as naloxone. These drugs can reverse the effect of overdoses, and there is a focus on making them as affordable as possible while increasing access to them (Secretary for Health and Human Services, 2018).

The third priority in the Opioid Strategy is that of public health surveillance and research. A goal of the HHS is to increase cooperation between public health authorities and law enforcement. To accomplish this, the HHS is working with Customs and Border Protection, so that when shipments of opioids are intercepted, the local public health authorities are alerted in order to help them best prepare for an upcoming wave of overdoses (Secretary for Health and Human Services, 2018).

Pain management is an incredibly important component in the discussion of finding lasting solutions for the opioid crisis. It is necessary to avoid creating dependence in the first place, including rethinking and revisiting the revolution that has occurred in pain management over the past several years. The Office of Assistant Secretary and the National Institute of Health (NIH) are working through the Interagency Task Force on Pain Management to implement a National Pain Strategy (Secretary for Health and Human Services, 2018).

Overdose Treatments

Morphine is an agonist at the mu-opioid receptor and by functioning as an antagonist at the mu-opioid receptor; drugs such as naloxone can reverse overdoses. Naloxone has saved tens of thousands of lives, but administration must occur shortly after an overdose (Volkow & Francis, 2017). There is a necessity for newer improved reversal drugs. The National Institute on Drug Abuse (NIDA) developed a Narcan Nasal Spray, which functions as an intranasal naloxone formula. This spray was an advancement in the field of treatments, as it would result in blood naloxone levels that were equivalent to if the naloxone had been administered parenterally. This drug is also available in an injection form. Some longer-term alternatives that will potentially be able to intervene against opioid-induced respiratory depression include 5-hydroxytryptamine type 1A (5-HT1A) agonists, ampakines, and phrenic-nerve-stimulation devices. These treatments would be most effective for those individuals that are at high risk for overdose (Volkow & Francis 2017).

Opioid Use Disorder Treatments

There is no immediate solution for opioid addiction treatment. To maintain long-term recovery, sustained treatment over a prolonged period is necessary. However, three medications that are

approved for opioid use disorder: methadone via methadone maintenance treatments, buprenorphine, and extended-release naltrexone (Volkow et al., 2014).

Methadone Maintenance Treatment (MMT) involves having the opioid-dependent individual orally consume a daily dose of methadone under medical supervision. This treatment method aids in decreasing criminal activity often associated with obtaining illegal drugs (Volkow & Francis, 2017). There has been a development with buprenorphine treatment, which functions as a partial opioid agonist, which will produce lower levels of the side effects when compared to other opioids such as oxycodone and heroin. NIDA collaborated with pharmaceutical industries to develop an implant, Probuphine, which would deliver doses on a weekly or monthly period to the individual. This is an initial step towards long-term treatment methods and would work well for patients that have had nonfatal opioid overdoses (Volkow & Francis, 2017). Extended-release naltrexone is a monthly injectable formula of the mu-opioid receptor antagonist that is also used to prevent opioid dependence. There has been much promise shown for vaccines against prescription opioids, synthetic opioids, and heroin. These vaccines would function by inducing antibodies to prevent opioids from entering the brain (Bremer et al., 2016).

CONCLUSION

The opioid epidemic was not created in a vacuum. Surgeon and author Atul Gawande stated in an interview that it was doctors who have started the epidemic and it began as an effort to better treat pain, something that had previously been undertreated (Kliff, 2017). Moving forward it is important for the American Medical Association to ensure that physicians who are practicing in the United States are actively monitoring their patients and have safe methods to report any suspicious patterns. It is also necessary to create and enforce policies for healthcare providers that reflect the guidelines that are put in place from organizations such as the Centers

for Disease Control and Prevention. Pharmaceutical companies have also fueled the epidemic by using aggressive techniques to boost prescriptions. The American Pharmacists Association should focus on research that provides safer alternatives to opioid use for pain and couple these less aggressive pain treatments with ensuring that for those that are currently addicted, there are alternative medications at an affordable rate. A look at socioeconomic factors is also important, as a lack of health insurance, poverty, and unemployment are associated with a higher prevalence of prescription opioid disorder (Godlee, 2017). No biological treatment will address the lack of economic opportunity, and this will require action at an institutional level. Many insurance policies do not cover addiction treatments, and many individuals facing this crisis lack insurance. Nationally, a look towards expanding Medicaid will aid in increasing access to health insurance and should cover not just treatment but also preventive care. To create a more comprehensive opioid strategy, it will be necessary to build coalitions and partnerships with all the stakeholders involved through a collective impact model to guide decision making and collaborative approaches.

From the public health perspective, one of the solutions for many of the issues involved with this epidemic is that of improving accessibility and surveillance of data at local levels. By having data-driven frameworks present at local levels, interventions will be more adaptive to their respective regions and can be monitored for successes. It will also promote collaboration between the different areas that are involved in finding solutions- research, industry, and government.

Throughout the history of medicine, one of the strongest allies in resolving public health crises has been the field of science. With regards to the opioid epidemic, science needs to be at the forefront of the discussion regarding treatment. It is necessary to increase inter-agency

collaboration and recognize the true extent that this crisis spans. This current epidemic is multifaceted and involves many different agencies: pharmaceutical companies, medical professionals, educators, border control agents, governmental agencies such as the FDA & NIDA, law enforcement, and scientists. Better coordination of community involvement and allocating funds towards appropriate resources are some initial steps that should be taken to combat this epidemic. Finding alternate solutions to pain management that do not involve the administration of addictive opioids is imperative. Looking forward, a public health approach that focuses on evidence-based scientific tools will help to end this current crisis and prevent it from reemerging in the future.

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