

**Treatment of Opioid Dependence and Overdose**Jessi Jeffries with Dr. Brian Cherrington

Physiology

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Oral Presentation

*Honors Program**Gillette, WY*

Every day in America, 90 individuals die from overdosing on prescription pain relievers or synthetic opioids. From 1999 to 2015, American deaths from opioid drug overdoses increased from 8,048 to 33,091 (National Institute on Drug Abuse, 2017). Approximately two million Americans in 2015 abused prescription pain relievers, which increased from 2014. Opioid receptors reside in the reward pathway of the brain, releasing the neurotransmitter dopamine, providing users with euphoria and analgesia. Long term drug use induces chronic constipation, drug tolerance, immune suppression, hormonal changes, and increased sensitivity to pain (Dennis, B., Naji, L., et al., 2014). Opioid use disorders also negatively impact an individual's mental status, increasing incidences of depression, anxiety, and suicide.

This review examines previous research to assess the physiological effects of opioid dependence and overdose, with analysis of treatment. For treatment of opioid dependence, Methadone and Suboxone are useful medications. The medications provide enough opioid receptor activity to avoid withdrawals, but not enough stimulation compared to prescription or synthetic opioids. Since Methadone and Suboxone reduce activity at the opioid receptors, the individual experiences less physical dependence. An additional medication can be used for acute overdoses; Naloxone, commonly known as Narcan, can rapidly reverse an acute opioid overdose by blocking the opioid receptors.

## **Treatment of Opioid Dependence and Overdose**

### **Introduction**

Every day in America, 90 individuals die from overdosing on prescription pain relievers or synthetic opioids, compounds used for pain relief and anesthesia. Opioid receptors reside in the reward pathway of the brain, providing users with euphoria and analgesia. The misuse of opioids steadily increased from 1999 to 2015. Chronic use of opioids leads to dependence and affects an individual physically and mentally. Long term drug use induces chronic constipation, tolerance, immune suppression, hormonal change, and hyperalgesia (Dennis, B., Naji, L., et al., 2014). Opioid use disorders also negatively impact an individual's mental status, increasing incidences of depression, anxiety, and suicide (Ashrafioun, L., Bishop, T., et al., 2017) (Hassan, A., Howe, A., et al, 2017). With an acute opioid overdose, Naloxone is used to counter the effects of the opioid and increase a patient's chance for survival. Methadone and Suboxone are medications available for treatment of opioid dependence. These medications elicit effects in the body similar to opioids to avoid withdrawals, and help the patient stop abusing the drugs. This review examines previous research to assess the physiological effects of opioid dependence and overdose, with analysis of treatment.

### **Severity of the Opioid Epidemic**

In the early '90s, providers prescribed opioids at large rates, not fully aware of the severe consequences due to pharmaceutical companies' assurance that these newer medications were not addictive. Before long, there was an epidemic of opioid misuse, leading to highly addicted users. Since then, overdose rates steadily increased every year (Figure 1 from the National Institute on Drug Abuse). For example, from 1999 to 2015, American deaths from opioid drug overdoses increased from 8,048 to 33,091 (National Institute on Drug Abuse, 2017).

## Deaths from opioid overdoses in America from 1999 to 2015

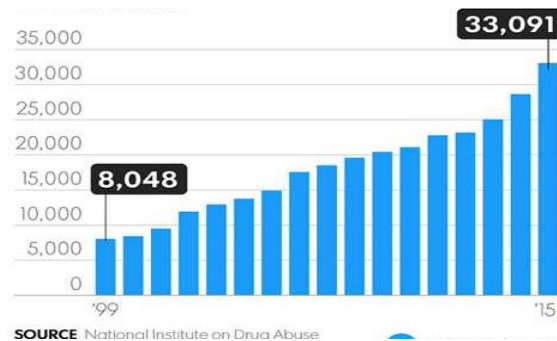


Figure 1: The graph provided by the National Institute on Drug Abuse illustrates the significant rise of American deaths as the result of opioid overdose.

Approximately two million Americans in 2015 abused prescription pain relievers, which increased from 2014. Heroin use also increased during this period, from 435,000 to approximately 591,000 Americans (Busch, S., Fiellin, D., et al., 2014). 21-29% of patients prescribed opioids for chronic pain misuse the medications, and 8-12% develop an opioid use disorder. Approximately 80% of people who use heroin, first misused prescription opioids (National Institute on Drug Abuse, 2017). To avoid escalation of the opioid epidemic, researchers study the cellular effects of opioids to better understand treatment options for opioid dependence and overdose.

### Cellular Mechanism of Opioids

The movement of calcium is a key component in the cellular mechanism of opioids. After ingestion or injection of the drug, the opioid molecule binds to a G-protein coupled receptor (GPCR), either mu, delta, or kappa receptors (specific activation of each receptor will be discussed below). Binding of the ligand to the GPCR elicits a conformational change, which activates a G-protein inside the cell composed of three subunits: alpha, beta, and gamma. During

this activation, the molecule guanosine triphosphate (GTP) binds to the alpha subunit of the G protein, and the unit dissociates from the beta and gamma subunits. This GTP-activated alpha subunit, activates the membrane bound enzyme phospholipase C (PLC). PLC catalyzes hydrolysis of membrane bound phosphatidylinositol 4,5-diphosphate (PIP<sub>2</sub>), which forms two second messengers: diacylglyceride (DAG) and inositol 1,4,5-triphosphate (IP<sub>3</sub>) (Salaun, C., James, D., and Chamberlain, L., 2004) (Jin, W., Lee, N., et al., 1994).

In the presence of calcium, DAG binds and activates protein kinase C, which then phosphorylates cellular proteins. This process is important for signal transduction to the nucleus. IP<sub>3</sub> diffuses to the endoplasmic reticulum (ER), where its own receptors reside. The activation of the IP<sub>3</sub> receptor on the endoplasmic reticulum, results in calcium moving out of the ER and into the cell, increasing the intracellular concentration of calcium. Calcium serves as an important second messenger for exocytosis, an energy-dependent process used to transport molecules out of a cell. The second messenger calcium also binds to calmodulin, a multifunctional protein. Activation of calmodulin increases enzyme activation and intracellular processes, including mRNA activation (Salaun, C., James, D., and Chamberlain, L., 2004).

Calcium influx into the cell initiates release of the neurotransmitter dopamine into the synaptic cleft, between the two neurons (Figure 2). As stated above, calcium is important for the process of exocytosis. The release of a neurotransmitter is accomplished via the docking of vesicles to the plasma membrane. The vesicle carrying neurotransmitters fuses with the presynaptic membrane via the interaction of SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptors) proteins on the intracellular and extracellular membranes of the presynaptic cell. The fusion between the vesicle and plasma membrane results in the release of the neurotransmitter into the synaptic cleft, and the vesicle membrane becomes part of the

plasma membrane (Figure 2, Neher, E. and Sakaba, T., 2008). Once dopamine is released into the synaptic cleft, it binds to receptors on the post-synaptic neuron, eliciting a response of pleasure, reward, and motivation.

## Communication between Neurons

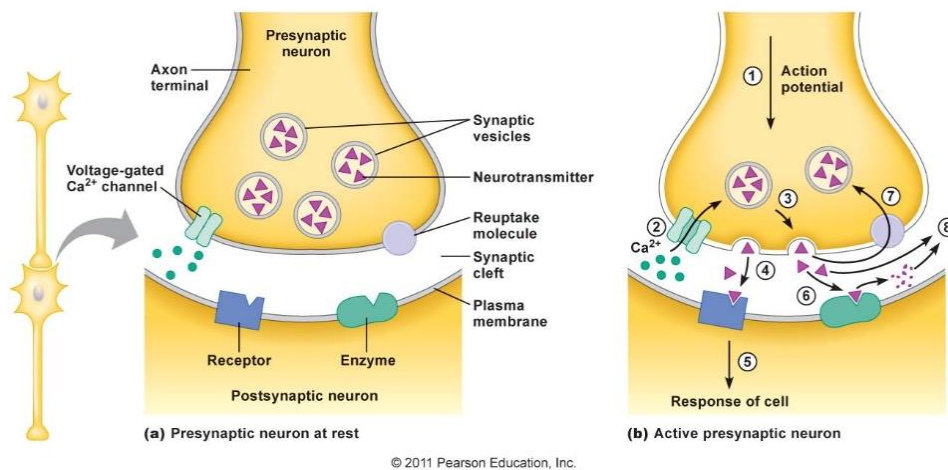


Figure 2: The process of communication between neurons with the influx of calcium, resulting in the release of neurotransmitters. Neurotransmitters bind to receptors on the post-synaptic neuron, eliciting a cellular response.

## Opioid Receptors

Opioid receptors consist of three GPCR subtypes: mu, delta, and kappa opioid receptors. All three receptors are found in components of the reward pathway, including the ventral tegmental area (VTA), nucleus accumbens, and prefrontal cortex (Figure 3).

## Reward Pathway

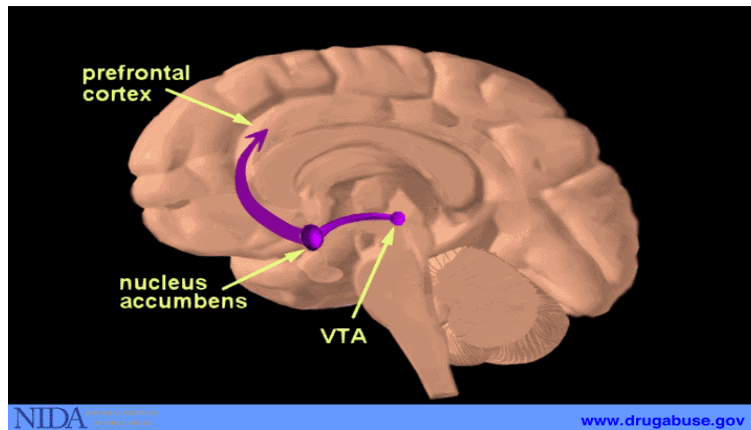


Figure 3: The reward pathway starting in the VTA, projecting to the nucleus accumbens, which propagates signals to the prefrontal cortex (National Institute on Drug Abuse, 2007).

Rich in dopaminergic neurons, activation of the reward pathway stimulates feelings of reward, motivation, and behavior. The VTA is a dopamine-rich nucleus that projects dopaminergic neurons, throughout the brain, primarily to the nucleus accumbens. From the nucleus accumbens, the signal is propagated to the prefrontal cortex which is responsible for complex cognitive behavior, personality expression, decision making, and moderating social behavior (Adinoff, B., 2004). Natural rewards such as food and sex—as well as substances including alcohol, caffeine, nicotine, opioids, amphetamine, cocaine, and marijuana—increase the extracellular concentration of dopamine (Adinoff, B., 2004).

Molecules that bind to these opioid receptors may be an agonist, a substance that binds to the receptor and elicits a response, or an antagonist which binds to the receptor and does not elicit a response, therefore, blocking other substances from binding. Additionally, two subtypes of agonists exist: endogenous or exogenous. An endogenous compound is made naturally within the body, including neurotransmitters and hormones. Exogenous compounds originate outside of

the body, but can be active inside the body, including drugs (Dhawan, B., Cesselin, F., et al., 1996).

### **Mu receptors**

Mu receptors reside in the dorsal horn of the spinal cord, periaqueductal grey of the brainstem, thalamus, and cortex, many of which are situated within the reward pathway of the brain. Beta endorphins, defined as endogenous opioid neuropeptides and peptide hormones, are released during exercise, pain, and stress. These substances have a high affinity for mu opioid receptors. Additionally, the exogenous drug Morphine has the highest affinity for mu receptors. Both beta endorphins and Morphine activate the mu receptors, eliciting an effect of reduced pain management, respiratory depression due to decreased response to carbon dioxide levels, euphoria, sedation, decreased GI motility (resulting in constipation), and miosis (constriction of pupils) (Dhawan, B., Cesselin, F., et al., 1996).

### **Delta receptors**

Delta opioid receptors derive from the olfactory bulb, cerebral cortex, nucleus accumbens, amygdala, and pontine nucleus. Enkephalins, which are endogenous opioid pentapeptides, have the highest affinity for delta receptors. Enkephalins are involved in pain perception, movement, mood, behavior, and neuroendocrine regulation. DPDE (D-Pen 2,5 enkephalin), an exogenous substance, also has a high affinity for the delta receptors. DPDE is used for research purposes only. After activation of the delta receptor, the body experiences spinal and supraspinal analgesia, as well as decreased GI motility (Dhawan, B., Cesselin, F., et al., 1996).

## **Kappa receptors**

Kappa receptors are found in the limbic system, hypothalamus, periaqueductal grey of the brainstem, and spinal cord. The endogenous peptide, dynorphin, has the highest affinity for the kappa receptors. Ketazocine, an exogenous drug used for research, has a high affinity for the kappa receptors, as well. Upon activation of the kappa receptors, users may experience spinal analgesia and inhibition of ADH (antidiuretic hormone) release. Users also experience hallucinations, dysphoria, overwhelming sense of dissatisfaction, anxiety, or restlessness. These receptors are the basis for research surrounding the mental effects of opioid use including, anxiety, depression, and suicide (Gannon, R., and Terrian D., 1992) (Dhawan, B., Cesselin, F., et al., 1996).

## **Activation of reward pathway**

The stimulants cocaine and amphetamine directly amplify the dopaminergic signal at the postsynaptic dopamine receptor. Cocaine increases synaptic dopamine concentrations by blocking the presynaptic dopamine transporter (Figure 4). The dopamine transporter is responsible for reabsorbing dopamine back into the presynaptic neuron. Cocaine binds to the dopamine reuptake transporter, preventing the reuptake of dopamine. The synaptic concentration of dopamine increases, and dopamine continues to bind to the dopamine receptors on the postsynaptic neuron (Adinoff, B., 2004).



## Cocaine Mechanism of Action

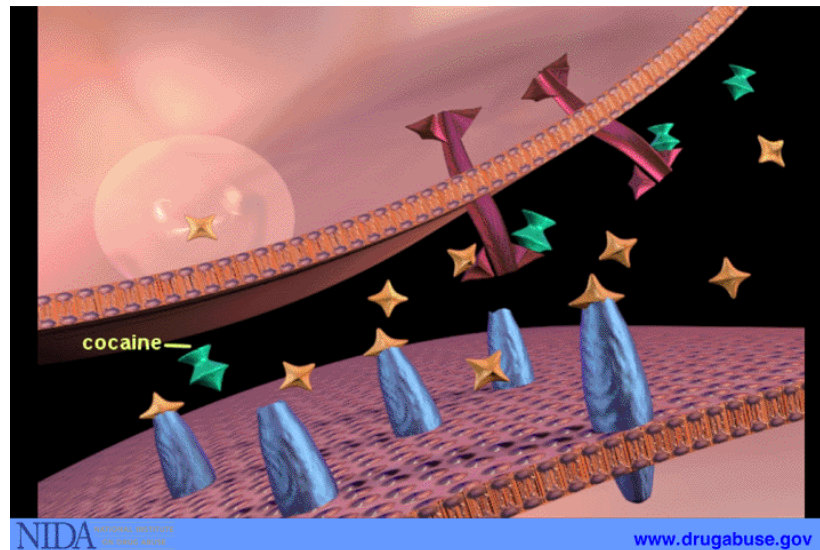


Figure 4: Cocaine (green) binds to the dopamine transporter (dark red), preventing the re-uptake of dopamine (orange) therefore, the synaptic concentration of dopamine increases, and continues to bind to the dopamine receptors (blue) on the post-synaptic neuron (National Institute on Drug Abuse, 2007).

The amphetamines increase synaptic dopamine primarily by increasing dopamine release from the synaptic vesicles. Cocaine and the amphetamines increase both the absolute concentration of dopamine in the synapse and the time interval that dopamine remains at the post-synaptic receptor site (Adinoff, B., 2004).

Various drugs activate the reward pathway indirectly via G-protein coupled receptors. Marijuana (THC), caffeine, and opioids activate G-protein coupled receptors by either acting as an agonist or antagonist. Marijuana acts as an agonist at cannabinoid receptors and caffeine activates the pathway as an antagonist at striatal adenosine A2 receptors. Opioids, such as heroin and morphine, activate G-protein coupled receptors by acting as an agonist at opioid receptors (Figure 5). Activation of opioid receptors increases dopamine concentrations in the synapse.

Dopamine binds to the receptors on the post-synaptic neuron, eliciting a cellular response in the reward pathway (Adinoff, B., 2004).

## Morphine Mechanism of Action

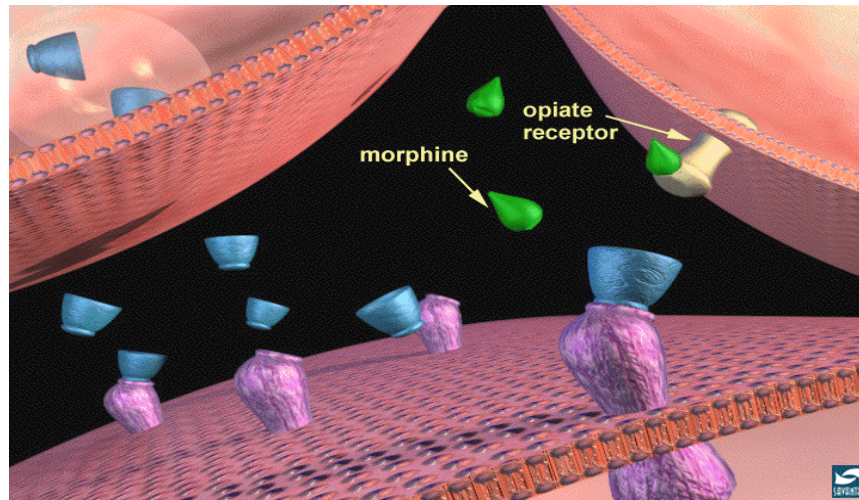


Figure 5: Morphine (green) activates opiate receptor, increasing the concentration of dopamine (blue). Dopamine then binds to receptors (purple) on post-synaptic neuron (National Institute on Drug Abuse, 2007).

## Physiological Effects of Opioid Use

Opioids have a substantial impact on all aspects of the body. The most common physiological effect from opioid use is constipation, occurring in 40-95% of users. The activation of mu and delta opioid receptors result in decreased GI motility, causing constipation. It can take only one dose of opioids to cause constipation. Although constipation seems like a relatively minor side effect, chronic constipation can lead to hemorrhoid formation, rectal pain, bowel obstruction, potential bowel rupture, as well as significant reduction in quality of life.

Consistent opioid use suppresses the immune system, which increases HIV risk and susceptibility for infections including hepatitis C and tuberculosis (Dennis, B., Naji, L., et al., 2014). Hormonal changes occur in men and women with chronic opioid use. Men experience decreased testosterone, libido, sexual dysfunction, and energy levels. Women may also

experience decreased estrogen levels, possibly inducing dysmenorrhea (painful menstrual cycle), sexual dysfunction, osteoporosis, and decreased bone mineral density. Interestingly, long term use of opioids can induce hyperalgesia, defined as the increased sensitivity to pain. This may be related to the enhanced release of excitatory neurotransmitters. Consistent opioid users may also reach the point of tolerance, which will reduce medication effectiveness and require ever-increasing dosage (Benyamin, R., Trescot, A., et al., 2008).

### **Mental effects**

Long term opioid use leads to higher incidences of anxiety, depression, and suicide. Opioid use is associated with the onset and recurrence of depression, increasing suicide risk. The activation of kappa opioid receptors induces hallucinations, dysphoria, overwhelming sense of dissatisfaction, anxiety, or restlessness. As the opioid epidemic increases, the rate of suicide increases. Suicide was the tenth leading cause of death in 2014 within the United States, which increased 20% from 1999.

Intentional self-poisoning, which accounts for over 5,000 suicides per year, is the most common means of poisoning admissions to emergency departments. Prescription opioid use is linked to poorly managed pain, which can independently be associated with suicidal thoughts and behaviors. When an individual has a poor quality of life, their depression may escalate, which increases the risk for suicidal thoughts and attempts. Anxiety disorders are more prevalent in chronic pain patients, requiring them to take long-term opioids, increasing the risk of depression and suicide (Ashrafioun, L., Bishop, T., et al., 2017) (Hassan, A., Howe, A., et al, 2017).

## **Treatment for Acute Opioid Overdose**

### **Naloxone**

The medication used for reversal of opioid overdose is Naloxone. Naloxone, commonly known as Narcan, is a medication used to rapidly reverse an acute opioid overdose. Naloxone acts as an antagonist at opioid receptors, with the highest affinity for the mu receptor. The substance acts as an antagonist at the kappa and delta opioid receptors as well, but with lower affinity (Adinoff, B., 2004). Narcan quickly returns the users respirations to normal, as they likely experienced respiratory depression when the opioid receptors were activated. The FDA-approved ways for administration of Naloxone are auto injectable and prepackaged nasal spray. Evzio is a prefilled auto-injection device that can be administered quickly into the outer thigh of the individual. The device provides verbal instructions, similar to an automated defibrillator, allowing families or emergency personnel to operate the device with ease.

Narcan, the most common form of Naloxone used in emergency settings, is a prepackaged nasal spray device that allows medication to be sprayed up one nostril as the individual is laying on their back. Narcan takes effect quickly, changing the individual's condition from unconscious, to alert and oriented in approximately five minutes. The medication lasts approximately 30-90 minutes, but if the person regresses to their unconscious state with shallow breathing, additional doses can be administered. After administering Narcan, medical personnel should monitor the user for two hours to monitor their breathing. Naloxone is a safe drug that only takes effects on individuals with opioid substances in their system (National Institute on Drug Abuse-Opioid Overdose Reversal, 2016).

## **Treatment for Opioid Dependence**

### **Methadone**

Acting as an agonist at the opioid receptors, Methadone has demonstrated positive results for 30 years in individual's dependent on opioids. The molecule binds to the receptors, eliciting effects similar, but weaker than opioids, helping suppress opioid withdrawals. Users take a daily oral dose of Methadone, while keeping close out-patient follow up with their doctors. A study performed by Eric Strain, et al. in 1999 found that a higher dose of Methadone showed a greater effect on the patient. The moderate dose range 40 to 50 mg of Methadone daily resulted in less detoxification completion compared to the higher dose of 80 to 100 mg daily. Following the study, 33% of the higher dose group completed detoxification, compared to 20% completion in the lower dose group. The drug continues to show promise for helping opioid dependence, as it has been identified to decrease drug use and transmission of human immunodeficiency virus infection (HIV). (Strain, E., Bigelow, G., et al., 1999).

### **Suboxone**

Suboxone is a substance composed of two medications, Buprenorphine and Naloxone, in a 4:1 ratio, respectively. Buprenorphine is classified as a partial opioid agonist, activating the receptor with the same characteristics as the prescription or synthetic opioids, but with less strength. Naloxone, as stated above, acts as an opioid antagonist, blocking opioids from binding to a receptor; there is no neuronal response when Naloxone binds to the receptor. Between the combination of Buprenorphine and Naloxone, Suboxone alleviates withdrawal symptoms. The medication provides enough opioid receptor activity to avoid withdrawals, but not enough stimulation compared to prescription or synthetic opioids. Since Suboxone reduces the activity at the opioid receptors, the individual experiences less physical dependence (Dennis, B., Naji, L., et

al., 2014) (Damian, A., Mendeson, T., et al, 2017). The difference in activity levels of Buprenorphine and Naloxone compared to Heroin are shown below in figure 6.

## Heroin, Buprenorphine, and Naloxone activation

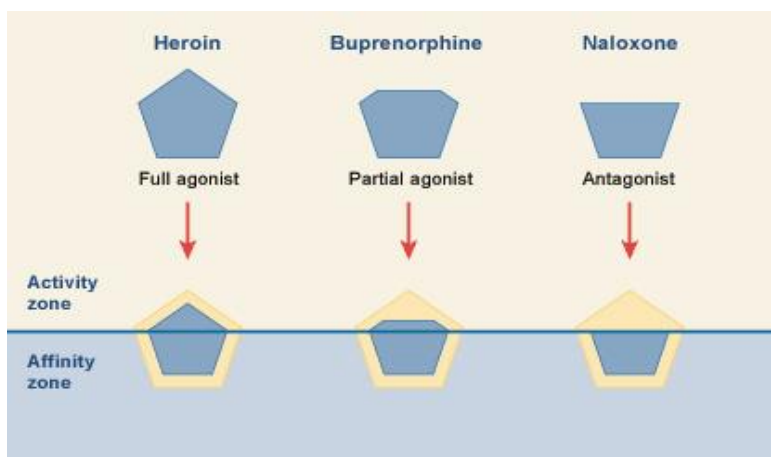


Figure 6: Comparison between Heroin, Buprenorphine, and Naloxone at the receptor (European Monitoring Centre for Drugs and Drug Addiction, 2005).

## Conclusion

On October 26, 2017, the opioid epidemic was declared a public health emergency in the United States. The opioid epidemic is a serious problem in the United States, with approximately 60,000 deaths due to overdose in 2016. Naloxone (Narcan) has the potential to save the life of an individual who has overdosed on opioids, but that is not the cure for this epidemic. With our current knowledge of opioids, researchers are studying additional medications and programs to minimize the opioid dependence and use. As the 2017 U.S. General Surgeon Jerome Adams states, “There is not one thing we can do to turn this opioid epidemic around, but we want to stop the deluge of people who are dying and help these people get connected with care.” In addition to the current medications available for opioid dependence and overdose, further treatment

options including detoxification programs, prevention, and general knowledge for the public and physicians will be the key to reducing the severity of this opioid epidemic.

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