

THE SHORT- AND LONG-TERM EFFECTS OF ADDICTING SUBSTANCES ON  
THE BRAIN

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## **Introduction**

Drugs are substances that have a physiological effect after introduction into the body or brain. Drugs of abuse have addictive properties that cause a high susceptibility of misuse and abuse, making these substances very dangerous. The incidence of use of addicting substances has increased significantly in the last decade, and the number of deaths each year from overdose has significantly increased as well (Substance Abuse and Mental Health Services Administration, 2017). Drugs of abuse are very common in the United States and continue to be a health concern in this country (Yasgar and Simeonov, 2014). This thesis is a narrative review of drugs of abuse and their effects on the body, particularly on the brain. The review will focus on a few of the most prevalent drugs of abuse: marijuana, nicotine, and prescription drugs, specifically opioids.

To begin, a brief discussion of drug administration is needed. There are several different routes of administering drugs. A few common routes are oral, rectal, topical, intranasal, transdermal, intravenous injection, intramuscular injection, subcutaneous administration, and inhalation (Meyer and Quenzer, 2013).

As described by Meyer and Quenzer (2013), oral administration involves taking a substance by mouth. This is a very common route of administration. To be administered effectively, the drug must be able to withstand destruction by the acid and enzymes in the stomach so that they can be absorbed by the small intestine. Oral administration utilizes first-pass metabolism, which is passing substances through the liver before being passed to the heart for circulation in the blood. Rectal administration involves absorption of substances by the blood vessels in the rectum, most often using a suppository. This route of administration is useful when patients are not able to take the substance orally.

However, substances that are absorbed in the lower portion of the rectum do not pass through the liver before circulation; whereas, substances that are placed deeper in the rectum do pass through the liver before circulation. Topical administration involves directly applying a substance to skin or mucous membranes. This method is useful for substances that target areas on the outside of the skin. Intranasal administration involves the use of the nasal cavity for the delivery of a substance. This administration usually involves a solution or mist so that it is easily passed through the nasal cavity.

Transdermal administration involves delivery of a substance across the skin. This method is effective because it does not have to be passed through the stomach, which results in at least some degradation, but still passes through the liver before circulating through the body. However, an issue for this method is the ability of substances to penetrate skin. Intravenous injection uses a vein to administer substances. This method very rapidly and very accurately administers and absorbs the substance, which is an advantage for patients that need a substance very quickly, but a disadvantage in that there is little time for response to complications or overdose of a substance. This method also requires sterile tools and techniques. Intramuscular injection uses a muscle, usually the arm or thigh, to administer a substance. The rate of absorption of this drug is slower than intravenous injection, but much quicker than oral administration. However, the rate depends on the rate of blood flow to the selected muscle and the volume of the substance that is injected, among other things. Sterile tools and techniques are required for this method. Subcutaneous administration administers substances between skin and muscle tissue. This method has a rate of absorption that is slower than both intravenous and intramuscular, but much quicker than oral administration. Sterile tools and techniques

are needed for this method as well. Inhalation uses the lungs to administer substances. This method is very common for administration of drugs of abuse because the large surface area of the lungs allows the substance to be absorbed very quickly, and the substance is circulated through the body quickly after administration. All of these routes of administration have different rates of absorption because of the different ways the substances can be administered and how they are impacted before they are absorbed, such as degradation by the liver and/or stomach acids and enzymes.

Next, it is important to understand the role of the brain's reward pathways and the neurotransmitter dopamine in the use and abuse of drugs. When any pleasurable behavior is performed, the probability of repeating that behavior is enhanced by the reward pathway in the brain. This reward pathway includes the ventral tegmental area (VTA), the nucleus accumbens, and the prefrontal cortex. Dopamine is released from neurons projecting from the VTA to the nucleus accumbens. The nucleus accumbens then sends projections to the prefrontal cortex, and these projections influence behavior. Dopamine is the primary neurotransmitter in this pathway and is the neurotransmitter most frequently associated with pleasure and reward (Volkow, Morales, 2015).

Dopamine is a catecholamine that is synthesized in the substantia nigra and in the ventral tegmental area (Baik, 2013). Dopamine acts as a neurotransmitter and exerts its effects on many parts of the brain, including the caudate-putamen, the prefrontal cerebral cortex, and the limbic system. Dopamine is synthesized from tyrosine and then encapsulated in a vesicle and transported by the vesicular monoamine transporter (VMAT), which is a vesicle membrane transporter. It is released from the vesicle by the process of exocytosis after a nerve impulse arrives at the pre-synaptic terminal. This

release causes behavioral activation. There are five dopamine receptors, D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>, and D<sub>5</sub>. D<sub>1</sub> and D<sub>5</sub> are similar, referred to as D<sub>1</sub>-like, and D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub> are similar, referred to as D<sub>2</sub>-like. All of these receptors are metabotropic and function using G proteins (Beaulieu, Espinoza, Gainetdinov, 2014). D<sub>1</sub>-like receptors stimulate the synthesis of cyclic AMP, which activates protein kinase A (PKA), and D<sub>2</sub>-like receptors inhibit the synthesis of cyclic AMP and activate potassium (K<sup>+</sup>) channels (Baik, 2013). Among other functions, dopamine is released in the reward pathway in the brain and is a very important component of this pathway.

The age of the person using drugs can influence the ultimate outcome, as the short and long-term effects of substances are different on adult and adolescent brains. As described by Yuan and colleagues (2015), adolescent brains are much more sensitive to substances because they are still developing. Because of this, substances, particularly drugs of abuse, can produce alterations to the brain structures and functions in adolescents that adults may not experience while using the same substance. Because of these factors, studies suggest that adolescents may be much more vulnerable to drugs of abuse than are adults (Yuan, Cross, Loughlin, Leslie, 2015).

These issues were taken into consideration in this review of the literature on a few of the most prevalent drugs of abuse: marijuana, nicotine, and prescription drugs, specifically opioids. Focus on these particular substances is justified by the following facts. Marijuana continues to be the most prevalent drug of abuse, especially among the 18-25 age range, with an increasing percentage of users starting during middle and high school (Substance Abuse and Mental Health Services Administration, 2017). Nicotine is one of the most prevalent legal drugs of abuse. It has strong addictive properties and can

lead to very serious health conditions (Substance Abuse and Mental Health Services Administration, 2017). Finally, prescription drug abuse is an increasingly prevalent and severe issue, behind only marijuana and alcohol in terms of abuse and misuse. Furthermore, overdoses from prescription drugs continue to be a leading cause of death (Substance Abuse and Mental Health Services Administration, 2017).

## **Methods**

For this review, PubMed was searched primarily between the years of 2013 and 2017, with one reference found from 2006. Search terms included: “short-term effects” of each substance, “long-term effects” of each substance, “e-cigarettes”, “long-term effects of e-cigarettes”, “review article” for each substance, etc. Statistics and information regarding these substances were also searched on the Centers for Disease Control and Prevention and National Institute on Drug Abuse websites.

## **Marijuana**

Marijuana is the most widely used illicit drug in the United States with a reported 22.2 million people using it as of 2015 (Goodman & Packard, 2015). In 2014, about 2.5 million people over the age of 12 reported using marijuana for the first time during the last 12 months, which averages to about 7,000 new users every day (Substance Abuse and Mental Health Services Administration, 2017). The controversy with legalization of this drug significantly limits its ability to be used for research purposes; however, its effects are currently being studied, specifically the effects of marijuana on learning and memory.

The marijuana that is widely used today comes from a plant known as *Cannabis sativa*. It is known mainly for its psychoactive component, delta-9-tetrahydrocannabinol or THC. This component acts on the CB1 receptors in the cannabinoid system (Meyer and Quenzer, 2013). These receptors are most prevalent in certain areas of the brain, such as the hippocampus, orbitofrontal cortex, amygdala, striatum, and cerebellum (Filbey et al., 2014). These cannabinoid receptors are metabotropic meaning that they work using G proteins, and they inhibit cAMP formation, inhibit voltage-sensitive Ca<sup>2+</sup> channels, and open K<sup>+</sup> channels. The activation of these receptors inhibits the release of many neurotransmitters in the brain (Meyer and Quenzer, 2013). Marijuana is primarily smoked or ingested (Sagie, Eliasi, Livneh, Bart, Monovich, 2013).

The *short-term* effects of marijuana on the brain and body have been extensively studied and are widely known. Marijuana impairs cognitive functions, such as learning and memory, and psychomotor functions, such as reaction time when driving a vehicle, and produces a euphoric “high” effect (Meyer and Quenzer, 2013). One study tested whether marijuana-related cognitive impairment was related to a failure in memory encoding or memory retrieval and determined that marijuana affects the encoding of memories and not the retrieval of them (Broyd, van Hell, Beale, Yucel, Solowij, 2016).

The *long-term* effects of marijuana on the brain and body have been less extensively studied and are not known as well as the short-term effects. It is hypothesized that marijuana may impair cognition in the long-term. One study by Battistella and colleagues (2014) suggested that it can alter regions that are linked to processing, both affective and executive, memory, and can cause decreases in volumes of the hippocampus and the amygdala, although the effects may differ from person to



person. The study also found that adolescents were more vulnerable to loss of white matter (Battistella et al., 2014). Another study showed that marijuana, as well as other substances of abuse, were associated with increased impulsivity and risk taking (Gruber, Dahlgren, Sagar, Gönenç, Lukas, 2014).

The most common class of marijuana users is the 18 to 25-year-old range, and many people report starting marijuana use in high school (Substance Abuse and Mental Health Services Administration, 2017). Since the brain is still developing during this time, adolescents that use marijuana could be more vulnerable to cognitive impairments than other users (Dougherty et al., 2013). One study by Dougherty and colleagues (2013) tested short-term memory recall among 14 to 17-year-old users and non-users and determined that recall was more impaired for marijuana users than for non-users.

Because of biological differences between the sexes, marijuana may affect males and females differently. However, to date, other gender identities (intersex, transgender, nonbinary) have not exclusively been studied. These issues may be particularly important during adolescence when females and males are physically changing. One study by Crane and colleagues (2013) examined the effects of marijuana on different cognitive aspects in males compared to females. This study concluded that there were little or no differences between the males and females studied, but they also reported that sample sizes were small and very few previous studies had been conducted on this issue (Crane, Schuster, Fusar-Poli, Gonzalez, 2013). Furthermore, according to a recent study by Sagie and colleagues (2013), there is a high correlation between marijuana use and schizophrenia, as well as a high risk of psychotic symptoms. This study also determined

that schizophrenia patients and marijuana users showed similar neuropsychological disruptions and cognitive deficiencies (Sagie, Eliasi, Livneh, Bart, Monovich, 2013).

## **Nicotine**

As described by The Centers for Disease Control and Prevention (2017), in the United States, about 40 million adults use cigarettes, and nearly 4.7 million middle school or high school students use cigarettes or an alternative tobacco product. Each day, about 3,800 young adults try their first cigarette. Around 500,000 people in the United States die each year from smoking or from secondhand smoke, and 16 million more struggle with a severe illness from smoking. These deaths and illnesses are some of the most preventable (Centers for Disease Control and Prevention, 2017).

In addition to cigarette smoking, e-cigarettes and vaping devices are becoming more common, especially among teens and young adults. Teens and young adults are more likely to use e-cigarette products than to use cigarettes. In 2016, about 2 million middle school and high school students in the United States reported using e-cigarettes in the last month (Centers for Disease Control and Prevention, 2018). About 6.3% of 10<sup>th</sup> graders reported using cigarettes in the last month compared to 14% reported use of e-cigarettes; the reported use in the last month for 12<sup>th</sup> graders was 11.4% for cigarettes and 16.2% for e-cigarettes (National Institute on Drug Abuse, 2016). This age range is also more likely to use cigarettes and other tobacco products if they are current users of e-cigarette products. Many users also do not know exactly what is in their device (National Institute on Drug Abuse, 2016). These new types of smoking devices have not been extensively studied yet so the long-term effects of them are still being discovered. They are advertised as a way to quit smoking; however, some studies are inconclusive, and

some studies have shown that users do not quit smoking but rather start using both e-cigarette products and cigarettes. These types of new products also contain nicotine, which is highly addictive, and other substances that can be harmful to the body (Centers for Disease Control and Prevention, 2018). The main concern is how little these devices have been studied and how little is known about the long-term effects of them.

As described by Meyer and Quenzer (2013), nicotine is a stimulant found in tobacco leaves and comes from two main sources of tobacco leaves, *Nicotiana tabacum* and *Nicotiana rustica* and was isolated from tobacco in 1828. This led to more automated manufacturing of cigarettes and is what is still used today. About 1-2 mg of nicotine, on average, is absorbed into the bloodstream, although cigarettes contain more nicotine. Nicotine acts on nicotinic cholinergic receptors (nAChRs), which are ionotropic receptors and consist of 5 subunits. The brain and parts of the autonomic nervous system contain these receptors. Activation of nAChRs leads to depolarization of the cell by  $\text{Na}^+$ , causing an action potential. Every time nicotine binds to the nAChRs, depolarization occurs, producing a stimulating response.

As described by Yuan and colleagues (2015), the *short-term* effects of nicotine in adolescents are a reduction in anxiety, an increase in locomotion, a strong reward effect, and weak withdrawal symptoms. Adults show a decrease in locomotion, a weaker reward effect, and stronger withdrawal symptoms compared to adolescents. The stronger and more positive effects that adolescents experience may make them more vulnerable to nicotine use during adolescence that could lead to dependence or addiction in adulthood (Yuan, Cross, Loughlin, Leslie, 2015).

As described by Yuan and colleagues (2015), the *long-term* effects of nicotine are different for adults and adolescents. Adolescents are more vulnerable to alterations in their brain structures and behaviors. Exposure to high doses of nicotine in adolescents decreases the activity of serotonin short-term and can lead to altered serotonin production later in life and causes upregulation of transporters for dopamine that can lead to an increase in the release of dopamine. Adults are less likely to have altered activity or production of serotonin or upregulation of transporters for dopamine than adolescents. Adolescents are also more vulnerable to decreased cognitive functions than adults. These include an increase in impulsivity, a shortened attention span, and increased anxiety, fear, and depression (Yuan, Cross, Loughlin, Leslie, 2015).

A study by Lerner and colleagues (2016) using lung cells from a human fetus showed that e-cigarette devices may increase the levels of mitochondrial reactive oxygen species. This was proposed to be in response to the inefficient electron transfer during the electron transport chain, which occurs in the mitochondria. This may have led to the production of reactive oxygen species from oxygen, rather than water, which would be produced during efficient electron transfer in the electron transport chain. Increased DNA fragmentation as exposure time increased was also seen in this study (Lerner, Rutagarama, Ahmad, Sundar, Elder, Rahman, 2016). This study also found that copper particles in the device used disrupted the mitochondrial membrane and mass, adenosine triphosphate (ATP) levels, and mitochondrial reactive oxygen species in the epithelial cells in the human airway. This study concluded that e-cigarette devices may increase DNA damage and oxidative stress on the mitochondria following long-term use (Lerner, Rutagarama, Ahmad, Sundar, Elder, Rahman, 2016).

## **Prescription Drugs**

The rate of overdose from prescription drugs in the United States is five times higher than it was in 1980, and the rate surpassed the number of deaths from automobile crashes in 2009. There has been a significant increase in the rate of deaths from overdoses in the last 10 years. In 1999, 30% of overdoses (where the drug was specified) were caused by opioids; in 2010, the number had risen to 60%, with 16,651 deaths from opioid overdoses (Behavioral Health Coordinating Committee, 2013). Prescription drug abuse is very dangerous because many people do not know that misuse or abuse can cause deaths from overdose (Harvin and Weber, 2015).

Prescription drugs are medications that require a prescription from a physician of some sort. Prescription drug abuse is defined as using prescription medicine in a way other than the way it was intended to be used (Harvin and Weber, 2015). The most common drugs that are misused or abused are stimulants, pain relievers (opioids), and sedatives (Lipari, Williams, Van Horn, 2017). However, this review will mainly focus on opioids.

As described by Ghelardini and colleagues (2015), opioids bind to opioid receptors that can be found in the central nervous system as well as the peripheral nervous system, especially in an area of the brain that deals with integrating the information that involves pain. The pain reliever effect that opioids exhibit is caused by their ability to reduce the pain threshold and cause detachment from pain emotionally. When opioids bind to these receptors, sodium ions interact with cyclic adenosine monophosphate (cAMP), which inhibits cAMP formation. Opioids also hyperpolarize target cells, which makes these cells less likely to generate an action potential and less

likely to release neurotransmitter, exerting the effects experienced upon taking opioids (Ghelardini, Mannelli, Bianchi, 2015).

Some *short-term* effects of opioids are temporary pain relief (Von Korff, 2013) as well as a strong sense of euphoria, drowsiness, and sedation. These effects are felt because opioids reduce the pain threshold and cause a detachment from pain emotionally. They also cause constriction in the pupils and impaired mental functions. However, one of the lethal effects of opioids is respiratory depression (Ghelardini, Mannelli, Bianchi, 2015).

The *long-term* effects are different for each category of prescription drugs. A few long-term effects of opioids are craving, tolerance, physical and physiological dependence, and dangerous use, including using several different pain relievers at the same time (Von Korff, 2013). A study by Atwood and colleagues (2014), showed that endogenous and exogenous opioids caused long-term depression of excitatory inputs in the dorsal striatum and the hypothalamus of rats and mice, and inhibitory inputs in the hypothalamus and hippocampus (Atwood, Kupferschmidt, Lovinger, 2014). A study by Pud and colleagues (2006), showed that the pain tolerance in chronic users/opioid addicts is significantly lower than that of non-users or even recovering addicts (Pud, Cohen, Lawental, Eisenberg, 2006). A study by Wang and colleagues (2015), showed that long-term exposure to opioids can lead to a disrupted resting state network, which is potential of the brain to allocate resources that are necessary for cognitive function. However, those undergoing methadone maintenance treatment showed less disruption than current users (Wang, Kydd, Russell, 2015).

## **Conclusion**

The three drugs on which this thesis focused (i.e., marijuana, nicotine, and opioid prescription medications) are important because they are among the most used substances in the United States (Substance Abuse and Mental Health Services Administration, 2017). This thesis highlighted recent research on these substances, and although much work has been done on these drugs, additional research is warranted.

For instance, although much is still unknown about marijuana and its effects on the brain and body, it is known that marijuana impairs cognitive functions, such as learning and memory, and psychomotor functions, such as reaction time when driving a vehicle, and produces a euphoric “high” short-term (Broyd, van Hell, Beale, Yucel, Solowij, 2016). It is also hypothesized that marijuana may be related to cognitive impairments in the long-term as well, and one study showed a decrease memory and volumes of the hippocampus and amygdala regions and decreases in white matter in adolescents (Battistella et al., 2014). Studies have also suggested that marijuana may have more severe cognitive impairment among adolescents, might affect males and females differently, and may be correlated with a higher risk of schizophrenia or other mental illnesses (Sagie, Eliasi, Livneh, Bart, Monovich, 2013). However, much more research is needed to determine the exact short-term and long-term effects of marijuana.

As described by Yuan and colleagues (2015), nicotine is also one of the most widely used substances. Adolescents have more positive and reinforcing short-term effects, while adults tend to have slightly more negative short-term effects. The long-term effects also differ between these two groups because of increased susceptibility

among adolescents. In adolescents, serotonin production and upregulation of dopamine may be altered leading to decreases in serotonin and an increase in dopamine, which are both less likely in adults. Adolescents are also more susceptible to decreased cognitive functions than adults (Yuan, Cross, Loughlin, Leslie, 2015).

Prescription drugs are becoming one of the most dangerous classes of illicit drugs, with one of the highest rates of death, by overdose, compared to other drugs of abuse. The most common drugs that are misused are stimulants, pain relievers, sedatives, and tranquilizers (Lipari, Williams, Van Horn, 2017). This review is mainly focusing on opioids.

Some of the short-term effects of opioids are temporary pain relief (Von Korff, 2013) as well as a strong sense of euphoria, drowsiness, and sedation. They also cause constriction in the pupils, impaired mental functions, and one of the lethal effects is respiratory depression (Ghelardini, Mannelli, Bianchi, 2015).

Some of the long-term effects are craving, physical and physiological dependence, dangerous use, and withdrawal (Von Korff, 2013). Three studies showed that endogenous and exogenous opioids caused long-term depression of excitatory inputs in the dorsal striatum and the hypothalamus of rats and mice, and inhibitory inputs in the hypothalamus and hippocampus (Atwood, Kupferschmidt, Lovinger, 2014); the pain tolerance in chronic users/opioid addicts is significantly lower than that of non-users or even recovering addicts (Pud, Cohen, Lawental, Eisenberg, 2006); and long-term exposure to opioids can lead to a disrupted resting state network, respectively (Wang, Kydd, Russell, 2015).



In conclusion, marijuana, nicotine, and prescription drug use, especially opioids, are the largest health concerns in the United States and are becoming very significant issues in this country because they are the most widely used substances of abuse (Substance Abuse and Mental Health Services Administration, 2017). More extensive research needs to be done on these substances of abuse as well as the rest of the substances of abuse, so that more can be known about the effects of these substances short- and long-term.

Future research studies could include longitudinal studies to help determine the long-term effects of the substances discussed in this review and other commonly abused substances, research studies that focus specifically on the effects of substances on adolescent brain development and how this compares to the effects on the adult brain, or research studies that focus on and visualize the physiological effects of substances of abuse.

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