Cannabis is the most commonly used illicit drug in the United States (Center for Behavioral Health Statistics and Quality, 2017). It is estimated that 13.9% of the American population (37.6 million) has used Cannabis at least once in their lifetime according to the 2016 National Survey on Drug Use and Health. The legal status of the substance has made experimental research difficult and, therefore, there is a limited amount of studies available to the scientific community. According to the Marijuana and the Controlled Substances Act (2014), cannabis has no known medicinal value and federal law prohibits the possession of cannabis. For this reason, researchers cannot simply provide the substance to participants and perform experiments. Therefore, researchers must get creative in how they perform experiments involving cannabis. Many times, cannabis research would be performed on animals using certain cannabinoids that make up cannabis. Researchers will also often make conclusions by comparing different groups, such as regular cannabis users and individuals who have never used cannabis. Regardless of the creative methodology that is used, the inability to provide human participants with a consistent dose of cannabis limits the validity of many experiments by potentially increasing the amount of confounding variables. However, there has been an increase in the amount of cannabis research with the recent legalization of both medicinal and recreational cannabis in many states. For example, a search of “cannabis” on ScienceDirect shows that there were 1,409 articles in 2009 with the term while there were 2,804 published in 2017.

An important reason as to why the amount of cannabis research has been increasing is actually very simple. Researchers want to know if cannabis has pharmacological utility in society. To solve this dilemma, many more questions must be asked. For example, one must study the side effects that accompany cannabis use and it must also be determined whether the benefits of cannabis outweigh its risks, such as dependence.
The current review is composed of three main topics to aid in the understanding of cannabis and potentially answer questions about the medicinal use of the substance. First, the composition of cannabis, the types of receptors cannabis induces, and the endogenous cannabinoids that have been discovered will be reviewed. Second, there will be a review of disorders associated with cannabis. This includes disorders that result from cannabis use, but also disorders and pathological diseases that benefit or are exacerbated by cannabis use. Finally, there will be a brief overview of cannabis use in society.

**Cannabis and the Endocannabinoid System**

Cannabis is composed of at least one-hundred cannabinoids and there are more that are currently being discovered (Jarvis, Rassmusen, & Winters, 2017). Δ⁹-tetrahydrocannabinol (Δ⁹-THC) is the most abundant cannabinoid found in cannabis and it is responsible for the psychoactive effects of its use (Mechoulam, 1970; Jarvis, Rassmussen, & Winters, 2017). The second most abundant cannabinoid in cannabis is cannabidiol (CBD) and, unlike Δ⁹-THC, it does not have a psychoactive effect in humans, but it does have anxiolytic and sedative properties (Malfitano, Basu, Maresz, Bifulco & Dittel, 2014; Galindo et al., 2016). The most common method of cannabis use in recreational users is smoking (Sznitman, 2017). Cannabis can also be vaporized or made into an edible form. Each type of use is similar in that cannabis is heated so that cannabinoids present in the substance are activated. If smoked or vaporized, the substance would enter the bloodstream quickly through the alveoli of the lungs. If eaten, the activated cannabinoids would enter the bloodstream through gastrointestinal organs at a slower rate compared to inhalation.

**History of Cannabinoid Receptors**
Suspicion of a specific cannabinoid receptor began when Howlett and Fleming (1984) observed the noncompetitive inhibition of the enzyme adenylate cyclase in neuroblastoma cell membranes after extracellular introduction of Δ⁹-THC. The experiment was followed by Howlett, Qualy, and Khachatrian (1986) who found that the inhibition of adenylate cyclase was dependent on a cannabinoid sensitive guanine-nucleotide-binding protein (G-protein) that could be inhibited by pertussis toxin. The existence of a specific cannabinoid receptor was finally confirmed when Matsuda, Lolait, Brownstein, Young, and Bonner (1990) cloned the CB₁ receptor and observed the expression of its complementary DNA in the central nervous system (CNS) of rats, especially in the hippocampus, cerebral cortex, hypothalamus, and amygdala. Gerard, Mollereau, Vassart, and Parmentier (1991) later cloned the CB₁ receptor in humans and found that the receptors were highly expressed in the brain and that the human CB₁ receptor shared 97.3% of the amino acid sequences found in the rat CB₁ receptor cloned by Matsuda and colleagues (1990), indicating that the CB₁ receptor has maintained similar properties throughout evolutionary history.

Soon after the discovery of the CB₁ receptor, researchers identified the presence of a different cannabinoid receptor. Munro, Thomas, and Abu-Shaar (1993) found a cannabinoid receptor that was highly expressed in macrophages of the spleen. This receptor was identified as the CB₂ receptor. Unlike the CB₁ receptor, which is highly expressed in the CNS, the CB₂ receptor is most present in peripheral tissue, especially in immune cells (Galiègue et al., 1995). However, expression of CB₂ was also found in the CNS, but only in active microglia, a macrophage-type cell found in the CNS (Carlisle, Marciano-Cabral, Staab, Ludwick, & Cabral, 2002).
From these reported findings, many concluded that the CB₁ receptor was the receptor through which Δ⁹-THC exerted its psychoactive effects, because of the high expression of the receptor in the CNS. As will be discussed later, the discovery of CB₂ receptors in peripheral tissue led many researchers to believe that the immune functions of Δ⁹-THC, such as its anti-inflammatory effect, was due to mechanisms involving the CB₂ receptor.

CB₁

The CB₁ receptor is the most studied cannabinoid receptor, because of its abundance in the CNS and its association with the psychoactive effects of Δ⁹-THC. The discovery and analysis of the CB₁ receptor allowed for the creation of new CB₁ agonists and antagonists that are useful in, not only localizing CB₁ receptors, but also discovering the mechanisms involved with the receptor.

Δ⁹-THC has been found to exert an effect on postsynaptic neurons by stimulating the neurons to release synaptic retrograde signals that influence the release of presynaptic neurotransmitters (Wilson & Nicoll, 2002). For example, binding of Δ⁹-THC on CB₁ receptors of a postsynaptic neuron may result in increased permeability to calcium ions by the opening of calcium ion channels in the dendrites or cell body of a postsynaptic neuron. The influx of calcium ions may result in the vesicle release of messengers into the synaptic space. Acting as a retrograde signal, these messengers would then bind to receptors on the presynaptic terminal thus influencing the regulation of neurotransmitter release from the presynaptic terminal. This described mechanism has been proposed for neurons in the hippocampus that release the neurotransmitter gamma-aminobutyric acid (GABA) where CB₁ agonists indirectly inhibit the release of GABA (Lupica, Hu, Devinsky, & Hoffman, 2017).
CB₁ receptors have also been located on presynaptic terminals and, therefore, a similar mechanism as described above may occur but more directly (Gaston & Friedman, 2017). For example, CB₁ receptors have been found to inhibit certain calcium channels located at presynaptic terminals (Felder & Glass, 1998). This inhibition would prevent an influx of calcium ions in the presynaptic terminal and a lack of vesicle-mediated neurotransmitter release. This cannabinoid mechanism is suspected in the observed reduction of acetylcholine and glutamate release from neurons of the hippocampus. In summary, CB₁ receptors have been linked to inhibition of neurotransmitter release through both intracellular and intercellular mechanisms.

Using an in vitro method, Glass, Dragunow, and Faull (1997) confirmed that CB₁ receptors were located mostly in the CNS, but specifically at great abundance in the frontal and temporal lobes as well as distributed localizations in the thalamus and basal ganglia. The finding that CB₁ receptor availability was greater in the frontal lobe is consistent with the altered mental state that many users report when using cannabis, because damage to the frontal lobe is associated with changes in personality and higher cognitive functions such as reasoning and decision making (Curran, Brignell, Fletcher, Middleton, & Henry, 2002). CB₁ receptor availability in the temporal lobe and thalamus is consistent with reports of mild hallucinations, because the structures are believed to be involved in the integration and perception of multiple sensory systems (Kolb, 2015). CB₁ receptor availability was increased in the hippocampus, which is part of the temporal lobe and is associated with explicit memory such as episodic memory (Kolb, 2015). Tasks requiring working and episodic memory, functions that greatly depend on the frontal lobe and hippocampus, were disrupted in human participants after smoking cannabis (Ilan, Smith, & Gevins, 2004). The availability of CB₁ receptors in the basal ganglia is interesting, because the structure contains the substantia nigra, a brain region containing
dopaminergic neuron which are degenerated in individuals who abuse amphetamines (Todd et al., 2016). Therefore, a question arises as to the role of this area in cannabis dependence.

Variation in cannabinoid receptors exists between individuals and, therefore, individuals may experience different effects from cannabis use. Colizzi et al. (2015) determined three genotypes for the CB₁ receptor: AA, AG, and GG by utilizing post-mortem human brains. They identified the genotypes of live human participants and tested their working memories. All participants had abstained from cannabis use for at least six months. The participants were assessed on their cannabis use prior to the six months and were placed into a cannabis using and a non-cannabis using group. Of the post-mortem brains used, individuals carrying the G allele (AG and GG) had significantly lower CB₁ receptors compared to AA individuals. This is a very important finding, because genetic variation can impact something as simple as the amount of receptors present in the CNS. Although there was no decrease in accuracy between cannabis users and non-cannabis users, cannabis users had a greater reaction time than non-cannabis users. The most exciting finding was that individuals who were cannabis users and carried the G allele had decreased accuracy when compared to individuals who were non-cannabis users and carried the G allele, AA cannabis users, and AA non-cannabis users. From the study, it can be concluded that certain individuals may be more susceptible to cognitive deficits from cannabis use depending on their genotype. This has implications toward medicinal cannabis use, because the effect of cannabis may vary between patients and, therefore, accommodations would have to be made accordingly.

Although the use of cannabis is often accompanied by cognitive deficits, the substance is useful for its anti-epileptic, anti-inflammatory, and pain-relieving effects (Robson, 2001). Therefore, it would be favorable if the cannabis’s psychoactive properties could be eliminated
without losing its medicinal value. Elevation of the COX-2 enzyme has been linked to an increase in cognitive deficits (Chen et al., 2013). Chen and colleagues (2013) discovered that the enzyme COX-2 is activated by the presence of $\Delta^9$-THC and, therefore, the researchers hypothesized that inhibition of COX-2 after injection of $\Delta^9$-THC would result in a reduction of cognitive deficits. Chen and colleagues (2013) injected mice with $\Delta^9$-THC and observed for cognitive deficits during a spatial learning task. Mice that were injected with a COX-2 enzyme inhibitor and mice that had the COX-2 gene eliminated displayed a reduction in cognitive deficits after injection of $\Delta^9$-THC when compared to mice that were injected with just $\Delta^9$-THC. Although these findings are limited to mice models, the study was a crucial step toward finding a cannabinoid-based medication with limited side-effects.

CB$_2$

As previously stated, CB$_2$ receptors are mainly localized in immune cells, such as B-cells and macrophages, but also hematopoietic stem cells that give rise to many immune cells (Malfitano et al., 2014). Therefore, it has been hypothesized that cannabis exerts its immunosuppressive activity mainly through CB$_2$ receptors (Gaston & Friedman, 2017).

A common method of determining the function of a receptor is to remove its expression and observe the effects in a cell, group of cells, or species. Ziring and colleagues (2006) used genetically modified mice lacking the gene for CB$_2$ expression and measured the availability of certain immune cells in the mice. The researchers found a reduced number of B cells in the marginal zone of the spleen, which are needed to remove potentially dangerous substances from the blood, and in the peritoneum, which are needed for proper immune function in many abdominal organs (Ziring et al, 2006). There was also a reduced number of memory T cells in the spleen and a reduced number of natural killer cells in the large and small intestines. It can be
concluded from this study that CB₂ receptors are essential for proper proliferation of B cells, memory T cells, and natural killer cells in the spleen and abdominal organs.

Malan and colleagues (2001) were curious as to how cannabis exerted its pain-relieving effect. The researchers knew that activation of CB₁ resulted in decreased perception of pain, but they hypothesized that CB₂ activation could result in a similar local effect because of the peripheral localization of the receptor. Malan and colleagues (2001) used thermal stimuli to produce pain in both paws of mice. Prior to the thermal stimuli, one group of mice were injected with a selective CB₂ agonist in one paw. These mice demonstrated decreased nociception and inflammation when compared to mice that were not injected with the CB₂ agonist. Nociceptive behaviors were not reduced in the contralateral paw that was given a thermal stimulus but not a CB₂ agonist injection, indicating that the CB₂ agonist exerted a local pain-relieving function. To ensure that the CB₂ receptor is involved in antinociception, mice were injected with a CB₂ antagonist. The CB₂ antagonist eliminated the antinociceptive properties of the CB₂ antagonist.

Ibrahim and colleagues (2005) continued to work with the selective CB₂ agonist and attempted to discover how the CB₂ receptor exerted its local antinociceptive function. The researchers observed keratinocytes, which are epidermal cells that make up a large portion of the skin, because they contain CB₂ receptors and release endogenous opioids (Ibrahim et al., 2005). The researchers hypothesized that endogenous β-endorphin is at least partly responsible for the local antinociception effect of CB₂ activation. Ibrahim and colleagues (2005) used a similar methodology as Malan and colleagues (2001) in that a group of mice and rats were injected with a CB₂ agonist prior to the painful stimuli. A thermal stimulus was presented to the paw of each animal and the time until the animal withdrew its paw was recorded (Ibrahim et al., 2005). A longer time until paw withdrawal was indicative of reduced nociception. Shortly after the
thermal stimuli, the animals were euthanized and the skin of their paws were analyzed. The researchers replicated the antinociceptive effects of the CB2 agonist, but they also found a significantly increased β-endorphin concentration in the skin tissues retrieved of animals treated with the CB2 agonists compared to controls. It can be concluded from Malan and colleagues (2001) and Ibrahim and colleagues (2005) that activation of the CB2 receptor results in a local reduction of nociception that is mediated partly by the local release of β-endorphin.

The antinociceptive effect of CB2 activation may not only be due to β-endorphin but also a reduction in inflammation. Jiang and colleagues (2016) wanted to understand how cannabis exerted its anti-inflammatory effect, specifically through CB2 receptors. The researchers hypothesized that activation of CB2 would result in increased efferocytosis which is the removal of apoptotic cells by phagocytic cells. Using an in vitro design, the researchers cultured macrophages and induced apoptosis in some by ultraviolet radiation. The non-apoptotic macrophages were then treated with a selective CB2 agonist and the rate of efferocytosis was measured. The researchers found that efferocytosis was increased after treatment of the CB2 agonist when compared to the control condition. It can be concluded that activation of the CB2 receptor in macrophages results in increased efferocytosis. This may be just one mechanism of CB2’s anti-inflammatory effect, however, it is an important one, because increased efferocytosis would result in a decrease in local inflammation. Nociception results from direct exposure to a painful stimulus, but it can also be exacerbated by inflammation of the affected area. This is why certain painful pathologies, such as sciatica, are often treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids that reduce inflammation. The observed increase in efferocytosis and reduction in inflammation (Quartilho et al., 2003) is a promising treatment for
many of these painful pathologies especially with the lack of psychoactive effects of selective CB2 agonists.

**Endogenous cannabinoids**

The existence of cannabinoid receptors in the human body raises questions as to why the receptors are present. These discoveries led researchers to ask the following question: are there endogenous ligands that bind to cannabinoid receptors and if there are, then how do their effects compare to exogenous cannabinoids.

Devane and colleagues (1992) found that the endogenous compound arachidonylethanolamide, or anandamide, competitively inhibited the binding of Δ9-THC to a cannabinoid receptor. Anandamide acts as a CB1 receptor agonist and results in similar psychoactive effects as Δ9-THC, although, it must be present at increased concentrations (Felder & Glass, 1998). This indicates that anandamide has a lower affinity to CB1 when compared to Δ9-THC. Anandamide has been found at high concentrations in many brain areas that are CB1 dense, such as the hippocampus, basal ganglia, and frontal cortex, but the compound has also been found in areas with low to undetectable CB1 density indicating that anandamide may have another endogenous function (Felder & Glass, 1998).

2-arachidonylglycerol (2-AG) is another endogenous CB1 agonist that has been found in the CNS (Wilson & Nicoll, 2002). 2-AG is found at a much greater concentration in the brain when compared to anandamide, although, it’s affinity to CB1 is about the same as anandamide (Felder & Glass, 1998). Due to the hydrophobic nature of endogenous anandamide and 2-AG, they cannot be stored in vesicles like many small molecule neurotransmitters. Instead, the compounds are either made on demand or stored as precursors that are quickly modified to an active state (Wilson & Nicoll, 2002).
Disorders

Cannabis Dependence

The DSM-IV-TR defines substance dependence as “a maladaptive pattern of substance use, leading to clinically significant impairments or distress” (American Psychiatric Association, 2000). The pattern of use must also accompany at least 3 out of 7 criteria for dependence. Criteria include tolerance, withdrawal, using larger amounts than planned, inability to decrease substance use, significant amount of time spent using the substance, interruption of daily activities due to substance use, and continued substance use even after the realization that use has resulted in physical or psychological issues.

The DSM-IV-TR defines withdrawal as physical or psychological effects that occur from stopping use of a substance (American Psychiatric Association, 2000). The effects must also be detrimental to regular daily functioning. Budney, Novy, and Hughes (1999) surveyed individuals who were at an outpatient facility for cannabis dependence. The participants were provided with word items that had been reported in previous cannabis withdrawal studies and that had been reported for other substance dependence disorders. The most reported items were the following: craving, irritability, nervousness, restlessness, depression, anger, sleep problems, strange dreams, appetite problems, and headache. Therefore, it seems that most of the withdrawal symptoms reported were of a psychological and behavioral nature rather than physical issues such as nausea or muscle spasms. Regardless, given that the participants were seeking treatment for cannabis dependence, it may be assumed that the withdrawal symptoms are of enough severity to cause issues in functioning.

The recent increase and improvement of imaging technology has allowed for the detection and localization of many receptors in vivo. Ceccarini and colleagues (2013) used a
radioactive ligand and positron emission tomography (PET) to compare the amount of receptors in the brain between chronic cannabis users and healthy participants. The researchers found an overall decrease in the amount of CB₁ receptors available in chronic cannabis users compared to healthy participants. The researchers also compared the amount of receptors available in different brain structures and found significantly less CB₁ receptors in the temporal lobe, nucleus of accumbens, and anterior cingulate cortex. Therefore, it was concluded that downregulation of CB₁ receptors occurs in chronic cannabis users. This is similar to findings of dopamine receptor downregulation from cocaine abuse, although, the extent of downregulation may not be equal to that of CB₁ receptors from cannabis abuse (Volkow et al., 1990). A decrease in CB₁ receptors in the nucleus of accumbens is interesting, because there has been recent evidence that the nucleus of accumbens is involved in motivation and reward through dopamine pathways (Basar et al., 2010). Therefore, it would be reasonable to hypothesize that abuse of cannabis results in over-excitation of neurons in the nucleus accumbens through CB₁ receptors. Due to the human body’s tendency for homeostasis, signaling in these reward and motivation neurons would result in decreased CB₁ receptor expression to prevent over-excitation. The nucleus of accumbens has been linked to autonomic functions, such as blood pressure regulation (Gasquoine, 2013). Cannabis is known to increase both heart rate and blood pressure in individuals, therefore downregulation in the nucleus of accumbens from chronic cannabis use may be another mechanism through which the human body strives for homeostasis and prevents episodes of tachycardia and hypertension.

Although, Ceccarini and colleagues found reduced CB₁ receptor availability in chronic cannabis users, the researchers left an important question unanswered: Is the effect reversible? D’Souza and colleagues (2016) also used a radioactive ligand and PET to measure CB₁ receptor
availability in human participants. However, the researchers were stricter in defining chronic cannabis users by using DSM-IV cannabis dependence criteria and four additional criteria that pertained to cannabis use as well as an exclusion of participants with other substance use or psychiatric history. Participants were scanned 8-24 hours after last use, after a 2-day abstinence while in an inpatient facility, and after a 28-day outpatient abstinence with frequent urine and blood test to confirm abstinence. Like Ceccarini and colleagues (2013), D’Souza and colleagues (2016) found an overall decreased in CB₁ receptor availability in cannabis-dependent participants. This significant difference disappeared after just 2 days of abstinence. This is evidence that CB₁ receptor downregulation may not be permanent. In fact, it seems that receptor availability returns to baseline rather quickly, even in participants who had smoked at least 30 cannabis joints in the past 30 days. Unlike Ceccarini and colleagues (2013) who found no difference in CB₁ density in the amygdala of cannabis users, D’Souza and colleagues (2016) found significantly less CB₁ receptors in the amygdala, a region associated with emotions, and the hippocampus. This is part of the increasing evidence that cannabis use has a large variety of effects on the brain and, therefore, effects on bodily functions, perception, cognition, and behavior. D’Souza and colleagues (2016) also surveyed participants at the time of the first can, 2-day abstinence scan, and 28-day abstinence scan and found that there was a negative correlation between CB₁ receptor availability and withdrawal symptoms. Therefore, many of the withdrawal symptoms reported by participants in Budney, Novy, and Hughes (1999) may begin diminishing in as little as 2 days of cannabis abstinence.

Epilepsy

Epilepsy is a disorder where individuals have reoccurring seizures due to an unknown etiology, traumatic head injury, or central nervous system infection (Newton & Preux, 2018).
There are many types of seizures, but all consist of an over-excitation of neurons in a certain area of the brain. For example, generalized seizures are seizures associated with over-excitation diffusely around the brain and may result in loss of consciousness and convulsions (Newton & Preux, 2018). Others, such as focal seizures, may occur in specific areas of the brain and may result in no symptoms or very specific symptoms, such as muscle twitching in a certain extremity or slight changes in vision (Newton & Preux, 2018).

There is evidence that cannabis has been used as treatment for epilepsy since Mesopotamian times (Russo, 2017). Although, recent literature has demonstrated inconsistent findings of an anticonvulsant effect with Δ⁹-THC treatment (Gaston & Friedman, 2017). These inconsistent findings may be a result in the variability of cannabinoid receptors as described by Colizzi and colleagues (2015. Another cannabinoid-based treatment for seizures could involve CBD which contains anxiolytic and sedative effects (Galindo et al., 2016).

**Depression**

Research on the effects of cannabis on depression has been inconsistent. There are studies that find anti-depressant effects of cannabis while others show that it has no effect or even exacerbates depression symptoms. For example, Khadrawy, Sawie, Abdel-Salam, and Hosny (2017) found that injection of Δ⁹-THC into depressed rat models did not change depressive symptoms. The researchers created the depressed rat model by injecting them with reserpine, a sympatholytic that has been known to induce depressive symptoms in humans and rats. Depressive symptoms in rats were determined by decreased locomotion in an open-field test as well as other behaviors such as rearing, grooming, and stretching. Injections of reserpine led to decreased locomotion in the open field test compared to control rats. Meanwhile, injections of both Δ⁹-THC in the depressed model rats showed no significant increase in locomotion. There
are obvious limitations to the generalizations that can be made from a study using rat models of depression, because although depression is accompanied by human behavioral changes, a significant part of its diagnosis deals with aspects of cognition that contain processes that are essentially impossible to determine in rats. This study hints at the importance of being able to manipulate cannabis doses in human participants. With the increase in cannabis legalization in some states, there may new studies that are able to answer questions about cannabis and depression with as little confounds as possible.

**Cannabis in American Society**

Cannabis has a controversial history in the United States. It was placed in the Controlled Substances Act in 1970 as a Schedule I substance by the United States Congress, making it illegal to grow, possess, or distribute cannabis (Marijuana and the Controlled Substances Act, 2014). Schedule I substances are deemed to have no known medical value. This prevented research on cannabis for many years, because of very limited legal suppliers of cannabis. Research could still be conducted on cannabis users in the United States, but it was limited by the inability to provide participants with cannabis of consistent purity and, therefore, most research was merely correlational. However, individual states have been decriminalizing cannabis possession since the 1970s. Currently there are eight states that have completely legalized the possession of cannabis for recreational use and 29 states that have legalized possession of cannabis for medical use (Carliner, Brown, Sarvet, & Hasin, 2017).

There are many complex issues that arise from “medical marijuana,” including the lack of research available to physicians and the inability of physicians to prescribe cannabis without breaking federal laws. The limited research available on cannabis makes it essentially unethical for physicians to prescribe the drug, because of the potential side effects and negative consequences that may accompany cannabis use. The issue of breaking federal law when
prescribing cannabis is also significant, because physicians and other medical providers are jeopardizing their medical licenses, which are essential for medical practice in the United States. In addition, many of the medications that medical providers prescribe are often in the Controlled Substances Act, so providers must be in good standing with the federal Drug Enforcement Agency (Marijuana and the Controlled Substances Act, 2014). Therefore, medical providers in states that have legalized possession of cannabis for medical use will often avoid using the word “prescribe” and instead use “recommend” to avoid federal legal issues. Meanwhile, patients cannot obtain cannabis from pharmacies, but instead obtain it from state-regulated medical cannabis dispensaries (Marijuana and the Controlled Substances Act, 2014).

There is obviously a disjunction between federal and state cannabis law. Federal laws may actually be causing more harm in these states, because of the possible provider malpractice that could occur by only recommending cannabis rather than prescribing. Another issue is that states must create their own laws and regulations for medical cannabis dispensaries, which is not an ideal situation in the medical field where consistency is an essential factor. A possible solution for these issues may be placing cannabis into another class of scheduled substances, thereby, allowing for the legal research of cannabis in all states, giving medical providers the appropriate responsibility when prescribing cannabis, and including cannabis into a large list of medications available in pharmacies that are federally regulated.

Cannabis Use

Although health benefits exist with cannabis use, there are many individuals who use the substance recreationally. Therefore, an important question to ask is: Why do individuals use cannabis recreationally? To answer this question, one must first distinguish cannabis use between medical and recreational cannabis users. Sznitman (2017) did just that by surveying and
comparing three different groups in Israel: recreational, unlicensed medical, and licensed medical users. An interesting finding was that licensed medical users comprised only about 6% of the total participants in the study and these users also vaporized their cannabis more often when compared to recreational and unlicensed users. This signifies that licensed cannabis users may be more health conscious about how they consume cannabis (Sznitman, 2017). Licensed medical users were also more likely to use cannabis alone when compared to the other two groups. This hints that the use of cannabis by licensed users is less likely to be associated with social influences and more likely to be a result of pain management or symptom relief. Overall, there was not a significant difference between frequencies of cannabis use between the groups and, therefore, the question as to why is still relevant.

Haug and colleagues (2017) asked medical cannabis users about their motives behind their use and, in addition, they also compared motives between younger, middle-aged, and older participants. The researchers gave participants 36 options as to why they use cannabis, but the questionnaire involved twelve different categories: enjoyment, conformity, coping, experimentation, boredom, alcohol, celebration, altered perception, social anxiety, low risk, sleep, and availability (Haug et al., 2017) Quantity and frequency of cannabis use was higher in younger participants. Younger participants also reported boredom more often as the reason for cannabis use when compared to middle-aged and older adults. A greater number of middle-aged adults reported sleep as a reason for cannabis use when compared to the other groups while older adults were more likely to use cannabis for medical reasons. This study is concerning, because it demonstrates that the group of individuals who least need cannabis, young adults, are the ones using the substance most often. Fortunately, according to the 2016 National Survey on Drug Use and Health, cannabis use decreases as individuals progress in age. Another reason for the high
rate of cannabis use in young adults is a lack of education and regulation. Due to the prohibition of cannabis, there is a black market that is widely available to younger adults. Unfortunately, this black market is accompanied by unrestricted access to unregulated cannabis as well as other harmful illicit drugs.

**Discussion**

Cannabis is made of over one-hundred cannabinoids with Δ⁹-THC and CBD as the most prominent and studied cannabinoids (Mechoulam, 1970; Jarvis, Rassmussen, & Winters, 2017). Δ9-THC exerts a psychoactive effect while CBD exerts an anxiolytic and sedative effect (Galindo et al., 2016). It has been proposed that Δ9-THC acts on post-synaptic neurons by generating retrograde signals and/or acts directly on pre-synaptic terminals to influence neurotransmitter release (Wilson & Nicoll, 2002; Felder & Glass, 1998).

CB₁ and CB₂ are the receptors activated by cannabis with CB₁ located mostly within the CNS and CB₂ in peripheral tissue. CB₁ is responsible for the psychoactive effects of with many of the receptors located in the frontal lobe, hippocampus, thalamus, and basal ganglia (Glass, Dragunow, & Faull, 1997). Individuals may experience different effects from cannabis use depending on their genotype (Colizzi et al., 2015). CB₂ seems to be responsible for proper immune cell proliferation, antinociception, and anti-inflammation (Ziring et al., 2006; Malan et al., 2001; Ibrahim et al., 2005; Jiang et al., 2016).

Anandamide and 2-AG are endogenous cannabinoids that have been found in areas that are dense in CB₁ receptors. Anandamide has also been found in areas that are low in CB₁ expression and, therefore, it is possible that endogenous cannabinoids also exert physiological effects outside of CB₁ and CB₂ receptors.
Withdrawal in cannabis-dependent individuals seems to result in psychological and behavioral effects, rather than physical issues (Budney, Novy, & Hughes, 1999). Cannabis-dependent individuals also had decreased CB1 availability in the brain when compared to healthy individuals (Ceccarini et al., 2013), although, this reduction returned to baseline after a 2-day abstinence (D’Souza et al., 2016).

There have been inconsistent findings for Δ⁹-THC treatment in both epilepsy and depression (Gaston & Friedman, 2017; Khadrawy et al., 2017). This places CBD as a potential treatment for the disorders. The inconsistency in results may be caused by a lack of ideal experimental methodology used, although, it is expected that the increased legalization of cannabis in certain states will allow for consistency in dose administration in human participants.

Federal law prohibits the growth, possession, and distribution of cannabis (Marijuana and the Controlled Substances Act, 2014). However, individual states have legalized its medicinal and recreational use. Physicians often have to recommend, rather than prescribe, cannabis, because of the risk of losing their licenses. This dissolves the liability placed on physicians and could potentially place patients in danger. Therefore, federal law may be exacerbating cannabis-related issues rather than preventing them. A reasonable solution to this problem and many other cannabis-related problems would be for the Drug Enforcement Agency to move the schedule classification of cannabis. This would allow for more research as well as limit the potential harm to American citizens.
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