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A Comprehensive Report on Marijuana: Focus on the Paso Del Norte Region

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The aim of the current review is to examine the evidence surrounding the therapeutic effects and health consequences associated with marijuana use. Repercussions that have emerged as a result of marijuana legalization in the U.S. are identified, including the impact of legalization on the healthcare system, motor vehicle accidents, and crime. Furthermore, the current review examines literature related to marijuana and tobacco use in order to differentiate the health effects of each substance. Lastly, the authors of the current review discuss the impact of marijuana in communities in the Paso Del Norte Region.

Brief History

The earliest record of medicinal cannabis use dates back to 4,000 B.C. in China where it was used as an anesthetic during surgical operations (Drug Policy Alliance, 2016_a). Records from 1,000 B.C. indicate that cannabis was used medicinally in India to treat anxiety (Drug Policy Alliance, 2016_a). In the 15th century, China listed cannabis as a painkiller in the world's oldest pharmacopeia, the *pen-ts'ao ching* (Zuardi, 2006). Records from Germany during the medieval times suggest that cannabis was used as an anesthetic for childbirth and toothaches (Drug Policy Alliance, 2016_a). By the 19th century, Europe and America published over 100 scientific articles regarding the therapeutic effects of cannabis (Zuardi, 2006). In the 1840s, a French doctor by the name of Jacques-Joseph Moreau began experimenting with the intoxicating properties of cannabis and suggested that cannabis was effective as a sleeping aid, effective for increasing appetite, and effective for suppressing headaches (Pisanti & Bifulco, 2017). Throughout the 19th century cannabis extracts were widely marketed (Savage et al., 2016). Furthermore, cannabis was added to the U.S. Pharmacopeia in 1850 as a treatment for a number of afflictions including mitigating pain and increasing appetite (Savage et al., 2016). Despite the

evidence highlighting the therapeutic properties of cannabis, congress passed the Marijuana Tax Act in 1937, beginning the federal prohibition of cannabis (Musto, 1972). The U.S. Pharmacopeia subsequently removed cannabis as a medicinal treatment in 1941 (Zuardi, 2006). Under President Richard Nixon in 1970, marijuana was categorized as a Schedule I drug, declaring that marijuana has high potential for physical and psychological abuse, and does not contain medicinal properties (Bilz, 1992). Cannabis has now been categorized as a Schedule I drug for over half a century.

Why Marijuana Was Made Illegal in the U.S. The most commonly cited explanation is related to Mexican immigration following the Mexican Revolution (Pagano, 2018; Ferraiolo, 2007; Musto, 1991). For example, in a Google search using the following search terms: "*why was marijuana made illegal in the U.S.*", nearly every article that populates refers to marijuana being banned due to the prejudices associated with Mexican immigrants and their drug of choice (i.e., marijuana). Discussions of marijuana being banned due to prejudices associated with Mexican immigration are also commonly discussed in peer reviewed journals. In a manuscript published in the Journal of Policy History titled, "*From killer weed to popular medicine: The evolution of American drug control policy, 1937–2000*", the author writes,

"*Domestic concern about marijuana originated in the Southwest, an area that saw an influx of Mexican immigrant laborers in the 1920s. Mexicans were thought to be prone to criminal and deviant behavior; during the Great Depression they became an unwelcome population and Southwestern states complained to the federal government about their marijuana use. In the early 1920s, New Orleans police claimed that marijuana use was responsible for a large number of crimes, particularly among the city's black population. The association between marijuana and politically marginal groups stirred fear about the drug's effects, helped*

to justify its regulation, and ultimately led to a "latent social consensus" that supported marijuana laws for several decades." (Ferraiolo, 2007, p. 156).

Scientific American journal and magazine published an article stating,

"The practice of smoking cannabis leaves came to the U.S. with Mexican immigrants, who had come North during the 1920s to work and it soon extended to white and black jazz musicians. As the Great Depression of the 1930s settled over America, the immigrants became an unwelcome minority linked with violence and with growing and smoking marijuana. Western states pressured the federal government to control marijuana use. The first official response was to urge adoption of a uniform state antinarcotics law" (Musto, 1991, p. 9).

Interestingly, marijuana was classified as a Schedule I drug for similar reasons. For example, John Ehrlichman, a top aide for President Nixon explained why marijuana was listed as a Schedule I drug, stating,

"You want to know what this was really all about? The Nixon campaign in 1968, and the Nixon White House after that, had two enemies: the antiwar left and black people. You understand what I'm saying? We knew we couldn't make it illegal to be either against the war or black, but by getting the public to associate the hippies with marijuana and blacks with heroin, and then criminalizing both heavily, we could disrupt those communities. We could arrest their leaders, raid their homes, break up their meetings and vilify them night after night on the evening news. Did we know we were lying about the drugs? Of course we did" (Downs, 2016).

Overall, there are other explanations for why marijuana was made illegal that have been documented. For example, one reason is that the paper pulp industry was booming as a result of the newspaper industry, thus, investors in the paper pulp industry were worried that hemp (a

product of cannabis), would replace paper pulp. However, reasons for banning marijuana aside from the prejudices associated with minorities are less discussed within the literature.

Current U.S. Legislation. Within the last two decades, more than half of the states in the U.S. have legalized medicinal marijuana use. Additionally, ten states (*Alaska, California, Colorado, Maine*, *Massachusetts*, *Michigan*, *Nevada, Oregon, Vermont,* and *Washington,*) and the District of Columbia have legalized recreational marijuana use for individuals who are 21 years of age or older (see Table 1). Despite the trend of marijuana legalization in many states, marijuana is categorized as a Schedule I drug on the federal level (declaring no medicinal benefits) and thus there are many barriers to researching marijuana. Arguably, lengthy statutory and regulatory processes imposed by the government have systematically impeded rigorous research on marijuana (Bostwick, 2012; Taylor, 2008). Investigators interested in conducting research on marijuana must undertake one of the most stringent review processes. This involves submitting an investigational new drug (IND) application to the U.S. Food and Drug Administration (FDA), contacting the National Institute on Drug Abuse (NIDA) to obtain an administrative letter of authorization (LOA), and applying for licensure to possess marijuana to the U.S. Drug Enforcement Administration (DEA) (NASEM, 2017). Dr. Orrin Devinsky is the director of the Comprehensive Epilepsy Center at New York University's Langone Health and has received approval from the FDA to investigate the use of marijuana for treating epilepsy. In an interview with Time Magazine, Dr. Devinsky describes his experience of receiving approval, "The DEA sent men with guns to my office to inspect" (Sifferlin, 2018). Dr. Devinksy goes on to explain that the DEA required the hospital to have a special alarm system to secure the marijuana, a special lock on the door of the room in which the marijuana was stored, and a safe

large enough that it required engineers to visit the room and ensure that the safe did not exceed the maximum weight capacity for the upper floor level in which it was stored (Sifferlin, 2018).

Importantly, on March 23, 2018, President Donald Trump signed the *Consolidated Appropriations Act of 2018.* This act protects medical cannabis patients and businesses in 46 states from federal intervention; the act does not include Idaho, Kansas, Nebraska, or South Dakota (H.R.1625, 2018). Presumably, Senators or Representatives in the latter states requested to not be included on the list. In May 2018, the VA Medicinal Cannabis Research Act of 2018 was passed and demands the Department of Veteran Affairs (VA) to conduct research on the effectiveness of medical marijuana for treating various afflictions (i.e., post-traumatic stress disorder and pain) in veterans enrolled in the VA health care system (H.R.5520, 2018). The latter act seemingly represents a shift in opinions about medical marijuana within the U.S. government. Specifically, receiving approval to conduct research on marijuana has been particularly difficult due to its classification as a Schedule I drug, thus, passing an act that demands research on marijuana is atypical.

Current Legislation in Bordering Countries. In the last decade, marijuana legislation has changed its status in countries bordering the U.S. For example, Mexico decriminalized the possession of small amounts of marijuana (i.e., less than 5 grams of dried marijuana) in 2009 with aims of reallocating law enforcement resources toward big-time dealers instead of minor consumers (Wilkinson & Marosi, 2009). Additionally, Mexico legalized non-psychoactive cannabis-based substances for medicinal purposes in 2017 (Osborne, 2017). Canada legalized recreational marijuana use nationwide on October 17th, 2018 (Gillies, 2018). Canada legalized recreational marijuana to eliminate illegal sales and create a profitable market (Team, 2018). The Prime Minister Justin Trudeau justified the legislation by stating the following, "*It's been*

too easy for our kids to get marijuana – and for criminals to reap the profits… today we change that. Our plan to legalize and regulate marijuana just passed the Senate" (Berke, 2018). Canada is predicting that the marijuana market will be a $65 billion industry by 2020 (Berke, 2018).

Canadians over the age of 18 will be able to purchase marijuana from federally licensed producers, grow up to four plants at home, and possess up to 30 grams of dried cannabis (Sapra, 2018). Provinces within Canada are allowed to set their own rules for how marijuana is sold (i.e., minimum age to consume marijuana or locations that are permitted to consume marijuana), however, the federal government has imposed guidelines that all provinces must abide by (Gillies, 2018). For example, packaging of marijuana products must be plain and must include strict health warning labels (BBC, 2018). Furthermore, the federal government imposed the following restrictions on advertisements: 1) promotions toward youth, 2) promotions depicting celebrities, and 3) promotions depicting characters or animals (BBC, 2018). Research suggests that tobacco advertisements are effective at increasing tobacco use in the youth (Henriksen, Flora, Feighery, & Fortmann, 2002; Moodie, MacKintosh, Brown, & Hastings, 2008), thus the intent of imposing restrictions on marijuana advertisements is to similarly prevent increases in marijuana use in the youth. The ease of access initiated by the legalization of marijuana in the majority of the U.S. and bordering countries may lead to a surge in marijuana use in the U.S. resulting in unexpected health consequences.

Current Prevalence of Marijuana Use in the U.S. The rates of marijuana use in the US have increased considerably over the last decade. Approximately five million people reported using marijuana daily in 2007 (Substance Abuse and Mental Health Services Administration [SAMHSA], 2014) and approximately eight million people reported using marijuana daily in 2013 (SAMHSA, 2014). In 2015, approximately 19.8 million (7.5%) Americans over the age of

12 reported using marijuana in the past month (Azofeifa, 2016). A recent poll estimated that approximately 35 million Americans are "regular marijuana users," defined as using marijuana at least one to two times a month (Marist Poll, 2017).

Despite the legal age of consuming marijuana being set to a minimum of 21 in many of the states within the U.S., the rates of marijuana use in youth attending U.S. high schools is alarming. The 2017 Monitoring the Future (MTF) survey conducted at the Survey Research Center in the Institute for Social Research at the University of Michigan. The MTF is a nationally representative survey that assesses the prevalence *of* licit and illicit drug use in 8th graders (N = 16,010), 10th graders (N = 14,171), and 12th graders (N = 13,522) (Johnston et al., 2018). MTF defines prevalence of drug use as the proportion of a population or subpopulation who have used a drug over a particular period of time. The 2017 MTF survey reported that marijuana is the most widely used illicit drug in youth. The prevalence of 12th, 10th, and 8th graders who have used marijuana in their lifetime is approximately 45%, 31%, and 14%, respectively. The former result suggests that nearly one out of every two students in high school will try marijuana by the time they graduate. *Daily marijuana use* (as indexed by using marijuana 20 or more times in the past 30 days) in 12th, 10th, and 8th graders was approximately 5.9%, 2.9%, and 0.8%, respectively. Furthermore, 71% of high school seniors reported that they do not view marijuana as harmful. Attitudes and opinions about marijuana legalization are not only improving in the youth, but seem to be improving in adults across the U.S.

Approximately 12% of Americans believed that marijuana should be legalized in 1969, approximately 31% of Americans believed that marijuana should be legalized in 2000, approximately 52% of Americans believed marijuana should be legalized in 2014, approximately 57% of Americans believed marijuana should be legalized in 2016, and approximately 61% of

Americans believed marijuana should be legalized in 2017 (Geiger, 2018; Ingraham, 2017). Considering the current rates of marijuana use and the trend toward legalization of recreational marijuana in the U.S., it is important to understand the chemicals within marijuana that are known to contribute to the positive and negative health effects associated with using marijuana.

Chemical Compounds in Marijuana

Marijuana contains over 400 chemicals (Lusk & Rutherford, 2017) and approximately 104 of these chemicals are cannabinoids (ElSohly and Gul, 2014). Cannabinoids are molecules that can bind to cannabinoid receptors in cells (NASEM, 2017). There are two primary cannabinoid receptors: 1) CB_1 which is primarily expressed in the central nervous system (Matsuda, Lolait, Brownstein, Young, & Bonner, 1990), and 2) CB_2 which is primarily expressed in the immune system (Galiègu et al., 1995). Research on marijuana has largely focused on examining CB_1 and CB_2 receptors in response to two popular cannabinoids, Delta-9 Tetrahydrocannabinol (THC) and Cannabidiol (CBD).

Δ^9 Tetrahydrocannabinol (THC). THC is the psychoactive compound within marijuana that produces the intoxicating state often referred to as "feeling high". This intoxicating state has been described as "a pleasant euphoria and sense of relaxation" (National Institute on Drug Abuse [NIDA], 2018). Furthermore, many individuals experience increases in appetite, increases in laughter, heightened sensory perception (e.g., brighter colors), and altered perceptions of time (NIDA, 2018). Importantly, the intoxicating state accompanying the consumption of THC is not always pleasant. For example, some individuals report experiencing heightened anxiety, panic, and fear; although the latter effects are more common when the individual is inexperienced or has consumed large or unexpectedly high potency doses of marijuana (NIDA, 2018).

Cannabidiol (CBD). CBD is a cannabinoid that is gaining a great deal of attention in the last decade because it contains many of the same therapeutic properties of THC, however, does not include the psychoactive components (Izzo, Borrelli, Capasso, Di Marzo, & Mechoulam, 2009). Thus, individuals can consume CBD as a treatment without the intoxicating side-effects.

Research on CBD has proliferated for this reason. CBD contains the same chemical formula as THC but has a minor difference in the atom arrangement (ElSohly and Gul, 2014). Scientists believe that the differences in the atom arrangement prevents CBD from binding to the receptors that THC binds to, making CBD non-psychoactive (ElSohly and Gul, 2014). Notably, THC and CBD can be extracted from marijuana and used to create a number of products such as tinctures/oils (e.g., liquid substance), topicals (e.g., lotions), and even edibles (e.g., "weed" brownies).

Methods of Consuming Marijuana

Smoking marijuana is the most common method of consumption. Marijuana is typically inserted into a pipe (commonly referred to as a "bowl") or rolled cigarette (commonly referred to as a "joint") and a flame is applied so that the marijuana combusts and releases smoke; the smoke contains the active ingredients and is subsequently inhaled. Schauer and colleagues (2016) examined a national sample (N = 4,269) of adults over the age of 18 and reported the methods of consuming recreational marijuana in current users (as indexed by use in past 30 days) was a pipe (49.5%); joint (49.2%); a bong, water pipe, or hookah (21.7%); a cigar wrap, referred to as a blunt (20.3%); edibles/drinks (16.1%); and vaporizers (7.6%). See Table 2 for explanations of the various methods of consuming marijuana.

Combusted vs. Ingested THC. Importantly, combusted (i.e., smoked) THC affects the body differently than ingested THC. Specifically, the potency, onset, and duration of the effects differs depending on the method in which marijuana is consumed (Carter, Weydt, Kyashna-Tocha, & Abrams, 2004; Ashton, 2001). For example, combusted THC is absorbed into the pulmonary circulation and reverted from the pulmonary vein back to the heart (Benjamin & Fossler, 2016). The combusted THC is subsequently distributed through the bloodstream systematically, without passing through the liver (Benjamin & Fossler, 2016). Combusted THC impacts the brain within seconds or minutes and thus psychoactive effects occur instantaneously and typically last for one to three hours (Ashton, 2001).

In contrast, ingested THC is metabolized by the liver and converted into a chemical that is much more psychoactive than delta-9 THC, referred to as 11-hydroxy-THC (Carter, Weydt, Kyashna-Tocha, & Abrams, 2004). Ingested THC may take approximately 30 minutes to a couple of hours before the psychoactive effects occur and the duration of psychoactive effects

lasts longer (Ashton, 2001). Importantly, cannabinoids are extremely lipid soluble and thus they accumulate in fatty tissues; the tissue elimination half-life of THC is approximately seven days and the complete elimination of a dose could take up to 30 days (Ashton, 2001).

The various methods of consuming marijuana are important in the context of medicine because each delivery method could serve a purpose contingent on the affliction that is being treated. For example, combusted marijuana is the quickest method of delivery and could be used to treat afflictions that need immediate relief (e.g., chronic pain, nausea, or spasms). Vaporizers could alternatively be used if patients are not comfortable with smoking marijuana. Additionally, edibles could be consumed if patients are not comfortable with smoking or vaping marijuana, however, edibles may not be the best option for a patient experiencing nausea. Thus, a tincture or topical created from THC or CBD oil is an alternative option for consuming marijuana. CBD topicals (e.g., lotions) are another route of administration and can be applied directly to localized areas of the body to relieve pain. It is important to note that manufactures of marijuana edibles or topicals are not regulated by the Food and Drug Administration (FDA) and safe levels of THC have not been established as of yet (Benjamin & Fossler, 2016). However, restrictions have been created to regulate the content of THC within edibles at the state level in marijuana-legalized states. For example, Colorado limited each "unit" of edible to a maximum of 10 mg of THC and each package of edible products is limited to maximum of 100 mg of THC (Parnes, Bravo, Conner, & Pearson, 2018). Although there are an abundance of marijuana-products being sold throughout the U.S., emerging research suggests that the dosage labels on many of these products may be inaccurate (Bonn-Miller, Loflin, & Thomas, 2017; Vandrey et al., 2015).

Bonn-Miller, Loflin, and Thomas (2017) examined the accuracy of CBD extract labels by purchasing 84 CBD products from 31 different companies on the internet. The authors reported that approximately 70% of medical marijuana products sold online contained higher or lower concentrations of CBD than the label indicated. Additionally, some of the products contained significant amounts of THC (the psychoactive compound in marijuana), suggesting that a patient consuming CBD could become unintentionally intoxicated. Of the 84 products purchased from the internet, 42% of the products were under-labeled (containing a higher concentration of CBD than indicated), 26% were over-labeled (containing a lower concentration of CBD than indicated), and only 30% contained the specified CBD content (within 10%). Similar findings were reported by Vandrey et al. (2015), who examined 75 different edible products (e.g., baked goods, candy, or beverages) and found that 60% of the products were over-labeled (containing lower concentrations of THC than indicated), 23% were under-labeled (containing higher concentrations of THC than indicated), and only 17% were accurately labeled. There is great variability in the labeling of non-FDA approved products however it is possible to have more accurate labels as is the case with other meticulously controlled FDA approved cannabinoid-based products.

FDA Approved Drugs. Four drugs are currently licensed by the U.S. Food and Drug Administration (FDA): 1) Dronabinol, is a synthetic analog of THC advertised under the name Marinol® and is currently listed as a Schedule III drug (FDA, 2015); 2) Nabilone is a synthetic analog of THC advertised under the name Cesamate® and is currently listed as a Schedule II drug; 3) Syndros® is a liquid form of Dronabinol and is listed as a Schedule II drug; and 4) Epidiolex® is the first FDA approved drug (approved in June, 2018) that contains natural extracts of cannabis instead of human made synthetic variants. Notably, the first three drugs that

were approved by the FDA were synthetic analogues of THC, referred to as cannabinoid receptor agonists. Synthetic analogues of THC are a class of molecules created by chemists who take the natural chemical composition of THC and slightly vary its chemical composition; thus, the molecules still bind to cannabinoid receptors in a similar manner as THC or CBD.

Dronabinol (Marinol®) is administered orally and available through prescription in the U.S. Specifically, Dronabinol is manufactured as a capsule containing synthetic THC in sesame oil. Dronabinol was approved by the FDA in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy. In 1992, the FDA approved marketing of Dronabinol for the treatment of anorexia associated with weight loss in patients with AIDS.

Nabilone (Cesamate®) is also an oral capsule that was approved for marketing by the FDA in 1985 and is prescribed to treat the same health afflictions as Dronabinol.

Syndros® is a liquid form of Dronabinol and is prescribed to patients experiencing chemotherapy-induced nausea and vomiting when conventional antiemetic therapies are non-responsive. Syndros® is prescribed for the treatment of anorexia associated with weight loss in patients with AIDS.

Epidiolex® is a concentrated CBD oil containing over 98% CBD and is prescribed to patients with two severe epileptic syndromes: Dravet and Lennox-Gastaut syndrome. Ironically, considering that Epidiolex® is a natural extract of cannabis, it is still classified as a Schedule I drug (declaring no medicinal benefits), despite research suggesting that Epidiolex® significantly reduces drug-resistant seizures by 42% in epileptic patients (Devinsky et al., 2017).

Importantly, the FDA is currently examining another natural cannabis-based product referred to as Nabiximols (Sativex®), an ethanol cannabis extract composed of a one-to-one ratio of THC and CBD (gwpharm.com). Nabiximols was approved in the United Kingdom in 2010 as

a prescription drug for mitigating multiple sclerosis-related spasticity, multiple sclerosis-related bladder symptoms, neuropathic pain, and even sleep disturbance (gwpharm.com). Although synthetic analogues of THC and extracts of THC or CBD are currently approved or further being investigated by the FDA, another class of synthetic drugs that are not approved by the FDA have emerged as a popular alternative to marijuana, referred to as 'synthetic marijuana'.

Synthetic Analogues of Marijuana (Spice or K2). Synthetic marijuana (e.g., spice, K2) is human made psychoactive chemicals that contain very potent activators of endocannabinoid receptors and are sprayed onto dried plant material to mimic the effects of marijuana (Vardakou, Pistos, & Spiliopoulou, 2010). These chemicals are referred to as cannabinomimetics, or synthetic cannabinoid receptor agonists that mimic the effects of marijuana (Hudson et al., 2010). Synthetic marijuana is commonly marketed by manufactures as "incense" or "herbal blends" as an attempt to deceive consumers (NIDA, 2015; Zimmerman et al., 2009). Synthetic marijuana is consumed by either smoking the dry plant material or vaping it in a liquid form (Blundell, Dargan, & Wood, 2017). Synthetic marijuana users are likely to be individuals who are seeking a cheaper alternative to marijuana or trying to pass a drug test (Drug Policy Alliance, 2016; Castellanos, Singh, Thornton, Avila, & Moreno, 2011). Synthetic marijuana is highly toxic and has emerged as a public health concern in the last decade due to its association with a number of adverse complications including *seizures* (Zhang, Patel, & Dani, 2018; Tait, Caldicott, Mountain, Hill, & Lenton, 2016; Lapoint, James, Moran, Nelson, Hoffman, & Moran, 2011), *kidney failure* (Zarifi & Vyas, 2017; Tait et al., 2016; Shanks, Dahn, & Terrell, 2012), *tachyarrhythmia* (Lapoint et al., 2011), and *mortality* (Tait et., 2016; Shanks, Dahn, & Terrell, 2012). The incidences of individuals requiring medical attention due to having an adverse reaction from synthetic marijuana has proliferated in the last decade.

The U.S. Customs and Border protection first encountered synthetic marijuana such as K2 and spice in 2008 (DEA, 2012). In 2009, 13 calls were made to U.S. poison control centers across 41 states regarding synthetic marijuana over-doses (DEA, 2012). In 2010, nearly 600 calls were made to U.S. poison control centers in the first 6 months alone (Johnson, Johnson, & Alfonzo, 2011) and consequently led to the Drug Enforcement Agency (DEA) introducing an emergency ban on five cannabinomimetics (i.e. cannabicyclohexanol, CP 47,497, JWH 018, JWH 073, and JWH 200) commonly found in synthetic marijuana. Despite having the ban in place, approximately two thousand calls were made to the poison control in 2013 and almost 8,000 calls were made to the poison control in 2015 (Drug Policy Alliance, 2016).

Synthetic marijuana (e.g., spice) is currently classified as a Schedule I drug under the Controlled Substance Act; nonetheless, synthetic marijuana is widely available online or at smoke shops throughout the U.S. because manufacturers of synthetic marijuana circumvent legislation by substituting banned cannabinomimetics with variants that are not yet prohibited (Hudson et al., 2010). That is, the manufactures slightly alter the chemical composition of a banned chemical and re-brand this newly created analog with a new marketing name. Notably, the products available on the market change rapidly and have a life cycle of approximately 12-24 months before being replaced by newer product (Gurney, Scott, Kacinko, Presley, & Logan, 2014). This quick turnover further hinders efforts to schedule the drugs at federal and state levels because newer products have emerged by the time the government bans older products. Moreover, manufacturers proceed to bypass laws by including the words "*Not safe for human consumption*" on the label of synthetic marijuana products. Overall, the innumerable problems associated with synthetic marijuana suggest that synthetic marijuana products are truly not safe for human consumption. In contrast, there is substantial evidence that many of the natural

cannabinoids in marijuana are safe for human consumption and are effective for treating a variety of health afflictions.

Marijuana Therapeutic Effects and Health Consequences

Therapeutic Effects. The National Academies of Sciences, Engineering and Medicine (NASEM) released a committee review in January 2018 examining the health effects of cannabinoids and concluded that a number of afflictions can be treated with cannabis. The NASEM (2017) committee categorized the weight of the evidence regarding cannabis or cannabinoid use for health conditions into five categories: 1) conclusive evidence, 2) substantial evidence, 3) moderate evidence, 4) limited evidence, and 5) no or insufficient evidence. For example, a therapeutic effect would be categorized as conclusive evidence only if there is strong evidence from randomized control trials to support the conclusion. Notably, several major findings emerged from the NASEM (2017) committee review. For example, the authors report that there is "conclusive" or "substantial evidence" that marijuana is effective for treating the following health afflictions: 1) marijuana is associated with significant reduction in chronic pain symptoms, 2) oral cannabinoids are effective antiemetics for treating chemotherapy-induced vomiting, and 3) oral cannabinoids are an effective treatment for multiple sclerosis spasticity symptoms.

The authors of the current review created tables categorizing all of the therapeutic effects reported in the NASEM (2017) committee review (see Tables 3 - 8). Additionally, we extended upon the findings from NASEM (2017) by identifying studies reporting the therapeutic effects of marijuana that have been published from 2016 to August 1, 2018 (see Table 9). A literature review was conducted and the following databases were searched: PsycInfo, Medline, Google Scholar, and Proquest Thesis and Dissertations. Reference sections within textbooks and peer-reviewed articles were searched in order to identify additional sources. The following search terms were used to identify articles: "cannabi*" and "marijuana." In addition, the latter search

terms were combined with the therapeutic effects and health consequences mentioned within the NASEM review.

Several key findings emerged when examining recent research (see Table 9). For example, a number of studies reported that marijuana was effective for treating chronic pain (Park & Wu, 2017; Fanelli et al., 2017; Savage, Romero-Sandoval, Schatman, Wallace, Fanciullo, McCarberg, & Ware, 2016; Boehnke, Litinas, & Clauw, 2016; Haroutounian et al., 2016), chemotherapy-induced vomiting (Badowski, 2017), and seizures in epileptic patients (Devinsky et al., 2018; Devinsky et al., 2017; Tzadok et al., 2016). Importantly, the NASEM (2017) committee review concluded that there is "insufficient or no evidence" that cannabinoids are associated with reductions in seizure activity in epileptic patients. Following this conclusion, an Arizona physician named Dr. Sue Sisley was quoted saying that it was "unsurprising" that the NASEM didn't find evidence of cannabis being effective for epilepsy because there is a lack of research due to marijuana's classification as a Schedule I drug (Downs, 2017). Dr. Sisley went on to state, "The federal government has systematically impeded efficacy studies," implying that it is extremely difficult to study the therapeutic effects of marijuana in a laboratory due to federal research barriers (Downs, 2017).

Although NASEM concluded that there is "insufficient or no evidence" that cannabinoids are associated with reductions in seizure activity in epileptic patients, we believe that the evidence to oppose this conclusion is convincing. For example, Devinsky et al., (2017) found that Epidiolex® significantly reduced drug-resistant seizures by 42% in epileptic patients. Furthermore, Devinsky et al., (2018) found that CBD reduced the median number of seizures in epileptic patients by approximately 51% in 12 weeks and 59% in 48 weeks. Striking evidence is reported by Tzadok et al. (2016) who examined the efficacy of cannabis oil treatments in young

children and adolescents (ages 1-18) that were diagnosed with epilepsy. Seventy-four patients who were resistant to more than 7 antiepileptic drugs were recruited and treated for at least 3 months with cannabis oil. Nearly 9 out of 10 (89%) patients reported reductions in seizure activity. Thirteen patients (17.57%) reported 75-100% reduction in seizure activity, 25 (33.78%) patients reported a 50-75% reduction in seizure activity, nine (12.16%) patients reported a 25-50% reduction in seizure activity, and 19 (25.68%) reported less than 25% reduction in seizure activity. The latter findings demonstrate unequivocal evidence that marijuana was not only effective, but also superior to many of the antiepileptic drugs currently on the market. Despite this evidence, marijuana is still classified as a Schedule I drug and declared to have no medicinal benefits. The evidence demonstrates the therapeutic effects associated with marijuana, nevertheless, an important caveat to consider is that marijuana is also associated with a number of health consequences.

Health Consequences. The health consequences associated with marijuana use were synthesized in the NASEM (2017) committee review and weighted using the standardized language provided in Table 3. Major findings reported within NASEM (2017) suggest that there is substantial evidence indicating that the frequency of marijuana use is associated with: 1) worsened respiratory symptoms and increases in bronchitis occurrences, 2) increases in the development of schizophrenia and other psychoses, and 3) lower birthrates in offspring exposed to marijuana while in the womb. The authors of the current review created tables categorizing all of the health consequences reported in the NASEM (2017) review using their standardized language to weight the evidence (see Table 10). Additionally, we extended upon the findings from NASEM (2017) by identifying studies related to each health consequence associated with marijuana that have been published from 2016 to August 1, 2018 (see Table 10).

Importantly, NASEM (2017) highlighted the health consequences associated with prenatal, perinatal, and neonatal exposure to marijuana, however, maternal outcomes associated with using marijuana were only briefly discussed. Gunn et al. (2016) conducted a meta-analysis examining maternal and child health outcomes associated with prenatal exposure to cannabis and reported that anaemia is the "*most widely discussed maternal outcome in cannabis-pregnancy literature.*" Specifically, the odds of women who used marijuana during pregnancy and developed anaemia increased significantly (pooled OR = 1.36, 95% CI = 1.10 to 1.69) compared to women who did not use marijuana during pregnancy. However, a caveat of the current findings highlighted by the authors is that most research on marijuana users involves concurrent users of tobacco and marijuana, thus ruling out a marijuana-only effect is often challenging (Gunn et al., 2016). Considering this caveat, we found it important to highlight research investigating the concurrent use of marijuana and tobacco; findings are presented later in this review.

The NASEM (2017) committee review also highlights that there is moderate evidence suggesting that marijuana use is associated with impairments in the cognitive domains of learning, memory and attention. Additionally, the review reports that there is limited evidence that marijuana use is associated with impaired academic achievement and educational outcomes. Similarly, existing research suggests that adolescents who use marijuana demonstrate cognitive disadvantages in comparison to adolescents who do not use marijuana (Jacobus & Tapert, 2014). However, it is important to note that the conclusions of such existing research cannot imply causation. That is, it is still unknown whether the observed cognitive disadvantages are associated with pre-existing differences or if the observed cognitive disadvantages are associated with using marijuana (Jacobus & Tapert, 2014). Findings that have been published since the

NASEM (2017) review also suggest that the observed cognitive disadvantages in adolescents may be associated with pre-existing differences instead of marijuana use (see Table 10). Specifically, Meier et al., (2018) examined 1989 twins from the Environmental Risk (E-Risk) Longitudinal Twin Study. The authors investigated the impact of the frequency of marijuana use and marijuana dependence on neuropsychological decline as indexed by intelligence quotient (IQ) scores. The authors found that twins who used marijuana more frequently than their co-twin did not score differently on 5-6 executive function tests (Ps > 0.10). The authors concluded that short-term marijuana use in adolescents does not cause a decline in IQ scores or impair executive functions. Notably, the authors explain that even when marijuana use reaches the level of dependence, there is still not a decline in IQ or executive functions. The authors of the study conclude that family background factors are the causal factor explaining why adolescent marijuana users typically perform worse on IQ or executive function tests than non-users.

Marijuana and Tobacco.

Concurrent Use of Marijuana and Tobacco. Over the past 5 decades the rates of tobacco use have decreased significantly (Centers for Disease Control and Prevention [CDC], 2016) however, the rates of concurrently using marijuana and tobacco are increasing. Schauer et al. (2015) examined the National Survey on Drug Use and Health (NSDUH) which includes data collected from a nationally representative sample of adults from 2003-2012. The authors assessed trends in overall co-use and examined demographic characteristics associated with co-use. The results suggest that there was a significant increase in the co-use of marijuana and tobacco among adults between 2003-2012. Specifically, marijuana use among tobacco users increased from 14.2% to 17.8% ($p < .001$). In contrast, tobacco use among marijuana users decreased from 74.3% to 69.6% ($p < .001$). The authors suggest that the increase in the co-use of marijuana and tobacco is attributable to increases in the prevalence of marijuana use among tobacco users. Furthermore, the authors suggest that increases in access to marijuana through legalization may subsequently contribute to the use of marijuana in tobacco users.

Similar findings were reported by Keyes et al. (2016) who analyzed data from the Monitoring the Future (MTF) survey, a nationally representative survey of high school students in the U.S. Keyes et al. (2016) examined the relationships between cigarette use and subsequent marijuana use among cohorts of 8th, 10th and 12th graders. Findings suggest that lifetime cigarette smoking in 8th and 10th grade was significantly associated with lifetime marijuana use ($\beta = 1.35$, 95% CI: 0.52, 2.18) in 12th grade. Thus, 8th graders who reported having used tobacco in their lifetime were more likely to report having used marijuana by the time they reached 12th grade. Many researchers have aimed to investigate why individuals co-use marijuana and tobacco. Although researchers have assessed reasons for co-use anecdotally by asking users to

self-report why they use both substances, recent studies have investigated the chemicals within each substance in order to determine if there are synergistic or additive effects that may be unconsciously contributing to co-use.

THC and Nicotine Combined. Nicotine is the primary reinforcing chemical in tobacco associated with addiction (National Institute on Drug Abuse [NIDA], 2012). Research suggests that THC and nicotine may interact synergistically. For example, findings from animal model research suggests that nicotine increases the rewarding effects of THC (Valjent, Mitchell, Besson, Caboche, & Maldonado, 2002) and subsequently may contribute to increased dependence on one or both substances (Ford, Vu, & Anthony, 2002; Peters, Budney, & Carroll, 2012; Ream, Benoit, Johnson, & Dunlap, 2008). In a study by Valjent et al. (2002), mice were given doses of THC alone, nicotine alone, or co-administered each substance twice a day, over a period of five days. Mice that were given both THC and nicotine experienced the acute depressant effects induced by THC (i.e., avoidance response, locomotor activity, heart rate, body temperature), and the effects were potentiated by nicotine. Additionally, rats co-treated with THC and nicotine experienced altered levels of fear, withdrawal, and tolerance behaviors. The latter results suggest that functional-biochemical interactions may be occurring after THC and nicotine exposure. The authors of the study concluded that a synergistic interaction between cannabinoid and nicotine receptor/neurotransmitter systems exists. Thus, the acute depressant effects induced by THC were potentiated by nicotine co-administration. Furthermore, the authors state that THC and nicotine co-administration could potentially be activating the endogenous dopaminergic and opioid systems, leading to decreases in tolerance and higher expression of THC physical dependence (Valjent et al. 2002).

Similar findings also suggest that marijuana and tobacco interact synergistically when consumed simultaneously. For example, González, Cascio, Fernández-Ruiz, Fezza, Di Marzo, & Ramos (2002) reported that endocannabinoid levels in the brain are altered when rats are provided chronic nicotine treatment. In contrast, there is pharmacological evidence suggesting that cannabinoids alter nicotinic-acetylcholinergic receptor responses in the brain (Oz, Tchugunova & Dinc, 2004). Anecdotal evidence reported from co-users of marijuana and tobacco was highlighted in a review by Kohut (2017) that examined the interactions between nicotine and drugs of abuse. Specifically, Kohut (2017) examined qualitative data suggesting that marijuana users tend to report smoking tobacco after smoking marijuana because tobacco enhances the effects of marijuana. These findings are supported in studies demonstrating that mice intoxicated by THC self-administer more nicotine (Valjent et al., 2002). Additionally, in a double-blind cross-over experiment by Penetar et al. (2005), ten male and ten female human subjects were given either a placebo or a 21 mg transdermal nicotine patch 4 hours before smoking marijuana. Significantly altered physiological (e.g., increased heart rate) and subjective effects (e.g., subjects self-reported that the effects of THC lasted longer) were identified in participants who were administered the nicotine patch in comparison to those who were administered the placebo. Although research suggests that nicotine may increase the rewarding effects of THC and thus may contribute to increased dependence on one or both substances, little is known about the chemicals in the smoke emitted from marijuana and tobacco that may contribute to the health consequences of co-use.

Mainstream (i.e., firsthand) and sidestream (i.e., secondhand) smoke. More than 480,000 deaths per year in the U.S. are attributable to tobacco use (US Department of Health and Human Services, 2014) and the American Lung Association estimates that secondhand tobacco smoke

causes approximately 7,330 lung cancer deaths among non-smokers per year (American Lung Association, 2016). Intuitively, one would expect that similar consequences would emerge as a result of smoking marijuana because marijuana smoke is emitted from burnt plant material and the smoke is typically unfiltered (e.g., smoked in a joint or pipe). Moir et al. (2008) compared the chemicals found in both mainstream (i.e., firsthand) and sidestream (i.e., secondhand) smoke of marijuana and tobacco. The authors assessed the smoke composition and identified carcinogens emitted from each substance. Moir et al. (2008) reported that nitrogen oxide, hydrogen cyanide, and aromatic amines (such as 1-aminonaphthalene and 4-aminobiphenyl) were present at levels of 3-5 times higher in marijuana mainstream smoke than tobacco smoke. Ammonia was approximately 20 times higher in marijuana smoke compared to tobacco smoke. Moreover, mainstream marijuana smoked contained lower concentrations of selected polycyclic aromatic hydrocarbons (PAHs) in comparison to mainstream tobacco smoke. In contrast, sidestream marijuana smoke contained higher concentrations of PAHs in comparison to sidestream tobacco smoke. Moir et al. (2008) concluded that marijuana contains many of the known carcinogens and other chemicals implicated in the respiratory diseases associated with tobacco use. Thus, it is imperative to understand the negative impacts that secondhand marijuana smoke may have on non-smokers. Research suggests that passive exposure to marijuana smoke may result in testing positive for marijuana in a drug screening (Cone et al., 1987; Moore et al., 2011).

Cone et al. (1987) sought to assess THC levels in the urine of individuals who were passively exposed to marijuana smoke. The authors conducted a series of studies in seven participants, five of which had a history of marijuana use but were abstinent for the past 14 days. The other two participants did not have a history of marijuana use. In study one, the five

participants with the history of marijuana use were exposed to a one-hour session in which a cigarette-smoking manifold machine generated the side-stream smoke of 16 marijuana cigarettes. In study two, the same five participants were exposed to a one-hour session in which a cigarette-smoking manifold machine generated the side-stream smoke of four marijuana cigarettes. In study three, two participants were exposed to a one-hour session in which a cigarette-smoking manifold machine generated the side-stream smoke of 16 marijuana cigarettes. Importantly, passive smoke exposure was conducted in an unventilated room and room air levels of THC were assessed frequently. The results suggest that passive exposure to the 16 marijuana cigarettes resulted in positive testing for THC in all of the subjects; exposure to the passive smoke of 4 marijuana cigarettes yielded infrequent positive results with low concentrations of THC detected. These findings suggest that passive exposure to marijuana can result in testing positive for marijuana, however, detectability is inconsistent if the passive exposure is low.

Moore et al. (2011) also analyzed THC levels in participants who were passively exposed to marijuana but in a less controlled environment. Specifically, participants attended a Dutch coffee shop where marijuana use is legal under strict conditions. Passive exposure was assessed using saliva samples that were collected before entering the coffee shop and at five additional time points (20min, 40min, 1h, 2h, and 3h). A final sample was collected 12-24 hours after leaving the coffee shop. The authors sought to assess at which time point THC levels were present. Notably, THC was detected in all of the participants at each time point (20min, 40min, 1h, 2h, and 3h) after entering the coffee shop. Other cannabinoids such as CBD and THC-COOH were not detected. These findings suggest that false positives in oral fluid results are possible following passive THC exposure.

Despite research suggesting that combusted marijuana contains many of the same carcinogens and other chemicals associated with respiratory diseases in tobacco smokers, not a single study has linked marijuana with tobacco related cancers such as lung cancer, colon cancer, or rectal cancer (Hashibe et al., 2006; Tashkin, 2005; Melamede, 2005; Sidney, Beck, Tekawa, Quesenberry, & Friedman, 1997). In fact, research has demonstrated that a number of the constituents within marijuana may have anti-tumoral effects that inhibit the growth of a variety of cancers such as lung cancer (Munson, Harris, Friedman, Dewey, & Carchman, 1975), skin cancer (Casanova et al., 2003), breast and prostate cancer (Sánchez et al., 2001), leukemia and lymphoma (McKallip et al., 2002), glioma (Sánchez, Galve-Roperh, Canova, Brachet, & Guzmán, 1998), and pheochromocytoma (Sarker, Obara, Nakata, Kitajima, & Maruyama, 2000). The latter findings suggest that the constituents within marijuana (e.g., THC) may counteract the tumorigenic effects of the procarcinogens in marijuana smoke. Furthermore, the lung function of 5115 young adults over the course of approximately 20 years (beginning from age 18 to 30) was assessed in a study published in the Journal of the American Medical Association examining risk factors for cardiovascular disease (Pletcher et al., 2012). The authors found that tobacco smokers demonstrated a decrease in lung function over time, whereas marijuana smoke produced "unexpected" positive effects. Specifically, low to moderate users of marijuana demonstrated increased lung capacity compared to nonsmokers. The authors reported that it was difficult to estimate the potential effects of regular marijuana use due to the sample having an insufficient number of regular marijuana users. Overall, there is still a current debate within the research as to whether the differential impacts of marijuana and tobacco on the lungs are truly due to marijuana having anti-tumoral properties or due to the variations in dosage. That is, the majority of cigarette smokers tend to smoke multiple times daily, whereas, the majority of marijuana users

tend to smoke a few times a month. In order to draw accurate conclusions regarding the health consequences associated with combusted marijuana, further research needs to be conducted examining heavy marijuana users who do not use tobacco.

Marijuana Legislation Repercussions

The legalization of marijuana has resulted in a number of unexpected outcomes. For example, reductions in opioid related deaths have been reported in states with liberal marijuana laws (Livingston, Barnett, Delcher, & Wagenaar, 2017; Powell, Pacula, and Jacobson, 2015; Hayes & Brown, 2014), reductions in prescription drugs for which marijuana could serve as a clinical alternative have been documented in states that have legalized medicinal marijuana (Bradford & Bradford, 2017), reductions in crimes such as homicide and assault have been reported in states that have legalized recreational marijuana (Morris et al., 2011), increases in fatal motor vehicle accidents involving marijuana-positive drivers have been reported in Colorado (Salomonsen-Sautel et al., 2014). Counterintuitively, recent evidence suggests that traffic fatalities decreased by approximately 10% in Nevada within the first year of legalizing recreational marijuana (Margiott, 2018).

Marijuana Legislation and Opioids. A national crisis currently exists in the U.S. due to opioid addiction or misuse. According to the National Institute on Drug Abuse (NIDA) more than 115 fatal over-doses occur daily in the U.S. (NIDA, 2018). Heroin is one of the most common contributors of fatal opioid related over-doses; however, prescription painkillers are also addicting and often misused. Powell, Pacula, and Jacobson (2015) compared states that have legalized medical marijuana with states that have not legalized medical marijuana. The authors reported that states that have legalized marijuana have also experienced decreases in both opioid addictions and opioid overdose deaths compared to states that have not legalized medical marijuana. Similarly, Shi (2017) examined state-level annual administrative records of hospital discharges during 1997–2014 and reported that medical marijuana legalization was associated with 23% ($p = 0.008$) and 13% ($p = 0.025$) reductions in hospitalizations related to opioid

dependence/abuse and the prevalence of opioid pain reliever overdoses. Monte, Zane, & Heard (2015) suggest that marijuana is a safe clinical alternative for opioids because it may help with pain control. Other studies have reported that CBD reduces the rewarding effects of morphine (Katsidoni, Anagnostou, & Panagis, 2013) and CBD reduces cue-induced heroin seeking in animal models (Ren, Whittard, Higuera-Matas, Morris, & Hurd, 2009). In sum, these findings suggest that marijuana may serve therapeutic value as a treatment for pain relief, opioid addiction, and substance abuse.

Effect on Doctors Prescriptions. Another repercussion following marijuana legalization is a decrease in prescription drugs that marijuana could serve as a clinical alternative. Specifically, Bradford and Bradford (2017) examined the prescriptions filled by Medicare Part D enrollees from 2010 to 2013 and focused on prescriptions for health afflictions that marijuana could serve as a clinical alternative. Medicare Part D is also referred to as the Medicare Prescription Drug Benefit Program and was developed to help beneficiaries pay for prescription drugs (Medicare, 2018). Notably, after medical marijuana laws were implemented, there was a national overall reduction in Medicare program and enrollee spending estimated to be $165.2 million per year in 2013. The authors of the study concluded that the legalization of marijuana significantly impacts prescription patterns and spending in Medicare Part D. Bradford and Bradford (2017) reported that prescriptions for painkillers written by doctors reduced by approximately 1,826 fewer doses (on average) per year after legalizing marijuana.

Marijuana Legislation and Crime. Findings related to the impact of marijuana legalization on crime have yielded conflicting results. Some research suggests that marijuana legalization may result in reductions in crime in areas that have legalized marijuana whereas other research suggests that legalization increases marijuana-related crimes (e.g., carrying

marijuana without a prescription). Morris et al. (2011) examined the relationship between medicinal marijuana laws and crime across the United States. Crime data from each state was gathered from the FBI's Uniform Crime Reporting Program. The crime data included Part 1 offenses such as homicide, rape, robbery, assault, burglary, larceny, and auto theft. The authors reported that medicinal marijuana laws were negatively associated with crime. Specifically, a crime reduction of 2.4% was observed in reference to homicide and assault. Non-significant findings were observed when examining robbery and burglary crimes. These findings suggest that medicinal marijuana laws may be negatively associated with certain types of crimes.

Freisthler et al. (2017) examined the relationship between marijuana density outlets and crimes in Denver, Colorado, during the time in which marijuana outlets were beginning to sell for recreational purposes. The authors analyzed 481 census block groups over the course of 34 months (Jan. 2013-Oct. 2015); January 2014 was the year when marijuana began being sold for recreational use. Three types of crimes were examined: 1) violence, 2) property, and 3) marijuana-specific crime (i.e. crime committed against the retailer). The density of marijuana outlets was not related to rates of violent crimes (murder, rape, robbery, and aggravated assaults) and the density of marijuana outlets within the census block was not related to property crimes rates. However, the density of marijuana outlets in spatially adjacent block groups was positively correlated to property crime. For marijuana specific-crime, higher densities of marijuana outlets within the census block and adjacent blocks was related to higher rates or marijuana-specific crime. These findings suggest that the effects of the proximity of marijuana outlets on crime do not occur within the block of marijuana retailers, but in adjacent areas. However, marijuana-specific crimes are associated with the proximity of marijuana outlets.

Another crime that is likely to increase as more states begin legalizing marijuana is Driving Under the Influence (DUI) of a controlled substance (i.e., marijuana).

Motor Vehicle Accidents. Motor vehicle crashes are the leading cause of death each year among young people ages 16- 25 in the United States (Azofeifa, Mattson, & Lyerla, 2015). The most frequently detected substances in fatal car crashes in the U.S. are alcohol (National Highway Traffic Safety Administration [NHTSA], 2013) and marijuana (Brady & Li, 2012). A number of studies suggest that marijuana use within a month of driving a motor vehicle is associated with two to six times higher risk of being involved in a motor-vehicle crash compared to unimpaired drivers (Asbridge, Hayden, & Cartwright, 2012; Li et al., 2012; Baldock, 2008; Beirness, Simpson, & Williams 2006; Ramaekers, Berhaus, van Laar, & Drummer, 2004; Bates & Blakely, 1999). Research examining the impact of marijuana legalization on motor vehicle accidents has yielded conflicting results. For example, Salomonsen-Sautel and colleagues (2014) examined the proportion of fatal motor vehicle accidents before and after legalizing marijuana in Colorado that involved alcohol-impaired (greater than the legal limit of 0.08 Blood Alcohol Content [BAC]) and marijuana-positive drivers. The results suggest that after legalizing marijuana in Colorado there was an increase in fatal motor vehicle accidents involving marijuana-positive drivers ($p < .0001$); there was no difference in the proportion of motor vehicle accidents involving marijuana-positive drivers in states that did not legalize marijuana. In contrast, recent data suggests that traffic fatalities have decreased by approximately 10% in Nevada in the first year of legalizing recreational marijuana (Margiott, 2018).

Notably, the impact of marijuana on driving performance is thoroughly documented within the literature. Driving under the influence of marijuana is associated with decreases in mean driving speeds, increases in weaving (within lanes), and increases in average distances

headway to preceding vehicles (Hartman & Huestis, 2013; Downey et al., 2013; Bondallaz et al., 2016; Anderson et al., 2010). However, it is important to note that a review by Sewell, Poling, and Sofuoglu (2009) found marijuana use only had "modest" impairments on actual road tests. The authors also reported that experienced marijuana users demonstrated "*almost no functional impairment*" under the influence of marijuana "*except when it is combined with alcohol*." The latter effects are explained in a number of studies, highlighting that drivers under the influence of alcohol tend to underestimate their degree of impairment; thus, they drive faster, increase attempts to overtake vehicles, and decrease their average distance headway to preceding vehicles (Robbe & O'Hanlon, 1993; Smiley, 1999; Sewell et al., 2009; Neavyn, Blohm, Babu, & Bird, 2014; Hartman & Huestis, 2013). In contrast, drivers under the influence of marijuana tend to overestimate their degree of impairment; thus, they driver slower, make fewer attempts to overtake, and increase their average distance headway to preceding vehicles (Robbe & O'Hanlon, 1993; Smiley, 1999; Sewell et al., 2009; Neavyn et al., 2014; Hartman & Huestis, 2013). Research suggests that alcohol and marijuana consumed independently at low doses does not yield sufficient driving impairments to rise to the level of a public health or safety concern, however, driving performance is dramatically impaired when low doses of the two substances are consumed simultaneously (Ramaekers, Robbe, & O'Hanlon, 2000; Hartman & Huestis, 2013; Sewell et al., 2009).

Ramaekers et al., (2000) recruited eighteen participants and had them consume either an alcohol placebo or a dose of alcohol designed to reach a peak BAC of 0.06-0.07 g/dl. Participants concurrently consumed either a low dose of marijuana (100 μg/kg dose of marijuana), a high dose of marijuana (200 μg/kg), or a marijuana placebo. Participants were accompanied by driving instructors while driving on the highway after consuming either the

placebo or the marijuana and alcohol combinations. Vehicles were equipped with additional driving controls so that the instructor could take control of the vehicle in case of an emergency. Driving performance tests assessed the number of times that the driver swerved between lanes and overall lane stability. Notably, driving performance was not impaired in the placebo and drug conditions in which alcohol or marijuana were administered independently. Conversely, driving performance was impaired significantly when both substances were simultaneously consumed and observed impairments increased as marijuana dosage increased.

In a study by Downey et al. (2013), 80 recreational marijuana users were recruited to participate in six double-blind counter-balanced experimental sessions that involved consuming varying doses of marijuana and alcohol, and subsequently driving in a simulator that mimics a natural driving environment. Participants in the study smoked marijuana cigarettes containing either 0% THC (placebo), 1.8% THC, or 3% THC. In addition, participants consumed sufficient alcohol to achieve 0% BAC (placebo), 0.03% BAC, or 0.05% BAC. The results suggest that the combination of both alcohol and marijuana produced the most driving impairments within the simulator.

Further research is needed in order to clarify conflicting findings related to the impact of marijuana legalization on motor vehicle accidents. However, substantial evidence suggests that marijuana combined with alcohol results in detrimental driving impairments. Drivers in the U.S. are legally allowed to drive after consuming alcohol when their BAC is less than 0.08%. A public health threat may arise when drivers mistakenly assume that driving under the influence of small amounts of marijuana and alcohol in combination will not severely impair their driving. This potential misunderstanding is likely to become a major public health concern as more states legalize the recreational use of marijuana.

Regional Impacts of Marijuana.

The Paso del Norte (PdN) region stretches across two countries and three states: El Paso and Hudspeth Counties in Texas, Doña Ana, Luna, and Otero counties in New Mexico, and the municipality of Cuidad Juárez, Chihuahua, México. The impact of marijuana in either one of these states or countries will have consequences on the region. Currently, none of the constituents of the PdN region have legalized recreational marijuana. However, the national trend toward the legalization of marijuana may still impact non-legal marijuana states including those in the PdN region. For example, Texas has not legalized recreational or medicinal marijuana. However, in 2015, The Texas Compassion Use Act was enacted to allow patients with intractable epilepsy to access low-THC cannabis (Texas Department of Public Safety, 2016). New Mexico became the twelfth state to allow medical cannabis with the Lynn and Erin Compassionate Use Act in 2007 (New Mexico Department of Health, 2018). The purpose is to allow the beneficial use of medical cannabis in a regulated system for alleviating symptoms caused by debilitating medical conditions. Most recently, México's congress in 2017 approved medical marijuana use and its pharmaceutical derivatives (Secretaría de Gobernacion, 2017). La Secretaría de Salud is responsible for the development and enforcement of public policies to regulate the medical use and upon completion of this paper, no such plan has been finalized. Appendix A includes the current laws on marijuana or marijuana derivatives impacting the PdN region.

Texas and Border Region. The Texas School Survey of Drug and Alcohol Use (TSS) assessed current use and attitudes about licit and illicit drugs in 49,069 students in grades 7-12 from districts across the state (Texas Department of State Health Services; DSHS, 2016). The results suggest that marijuana remains the most widely used illicit drug among Texas youth, that

is, approximately 20.8% students reported using marijuana in their lifetime and 12.2% reported using marijuana in the past-month preceding the survey. Furthermore, 21.4% of youth in the border region of Texas (the study included three districts in El Paso County) reported using marijuana in their lifetime and 12.8% reported using marijuana in the past month. In regards to frequency of marijuana use, 1.6% of the participants reported everyday use, 2.0% of the participants reported several times a week, 2.6% of the participants reported several times a month, 3.1% of the participants reported about once a month, and 3.3% of the participants reported about once a year.

Reports for Region 10 of Texas (El Paso County included) from different law enforcement agencies report that marijuana and methamphetamine are the most trafficked drugs for this area. According to the West Texas High Intensity Drug Trafficking Areas (HIDTA), marijuana is currently priced between $225-300 per pound in El Paso (Texas Prevention Resource Center [TPRC], 2018). Furthermore, CBD advertisements are proliferating across storefronts in El Paso. CBD is currently being sold as gummies (see image 1), e-liquids (see image 2), and oils at convenience stores, smoke shops, supermarkets with an emphasis on organic food, and even at pharmacies. Furthermore, a pharmacy in El Paso (Surecare Specialty Pharmacy) is the first businesses in El Paso to begin producing its own line of over-the-counter CBD products.

Image 1: CBD Gummies purchased at 7-Eleven Store in El Paso, TX on July 23, 2018.

Image 2: CBD E-liquid purchased at vape shop in El Paso, TX on July 17, 2018.

In 2014, there were a total of 30,088 solid pounds of marijuana seized in El Paso, TX (TPRC, 2018). In 2015, there was approximately 21,543 solid pounds of marijuana seized in El Paso, TX (Texas Prevention Resource Center Region 10, 2018). In 2016, there was approximately 13,299 pounds of marijuana seized in El Paso, TX (TPRC, 2018). The latter results may suggest that the amounts of marijuana seized in El Paso each year are decreasing.

El Paso County recently approved the *First Chance Program*, preventing individuals from being arrested if they are caught with less than 4 ounces of marijuana and it is the first

offence (Claster, 2017). Under the First Chance Program, individuals who are caught with less than four ounces of marijuana will have the option to complete eight hours of community service and pay a $100 fine. Importantly, if the first time offender does not complete the program within 60 days or declines the option to complete the program, they will be arrested. As of June 2018, Aliviane Inc. Treatment Resources, were treating 144 adolescents for mainly marijuana misuse (TPRC, 2018).

Individual employers have approved policies related to marijuana or illegal substance use throughout the PdN region. Appendix B includes the policies related to marijuana or illegal substance use for El Paso's top employers (i.e. El Paso Independent School District, Fort Bliss, The University of Texas at El Paso, and Ysleta Independent School District).

New Mexico Counties. The prevalence of marijuana use in New Mexico and surrounding counties is very high. According to a 2015 survey of 15,624 New Mexican youth from grades 9-12, approximately 1 out of 4 students (24.4%, CI: 23% to 25.9%) reported using marijuana within the 30 days preceding the survey (NM-IBIS, 2018). Furthermore, approximately 1 out of 5 (19.9%, CI: 17.1% to 23.1%) of youth in Doña Ana County (the county in closest proximity to El Paso, TX) reported using marijuana within the 30 days preceding the survey (NM-IBIS, 2018). In Otero and Luna Counties, it was reported that 30.7% and 23.3% of youth used marijuana in the past 30-days, respectively.

West Texas High Intensity Drug Trafficking Areas (HIDTA) reports as of 2018, marijuana prices range between $240-300 per pound in Las Cruces, NM (TPRC, 2018). According to the New Mexico Department of Health (2018), as of March 31, 2018, there were 50,954 active patients in the Medical Cannabis Program, purchasing an average amount of 31.78 units (one unit of usable cannabis consists of one gram of the dried leaves and flowers of the

female cannabis plant, or 0.2 grams of THC for cannabis-derived products). At the same time point, Doña Ana County had 3,945 patients, Otero County had 1,457 patients, and Luna County 299 patients enrolled in the program.

Cd. Juárez, Chihuahua, Mexico. In a study published in 2016, the marijuana use among 7^{th} – 12^{th} graders in the state of Chihuahua was reported at 11.9% lifetime use (Velazquez et al., 2016). In Cd. Juárez, 12.3% of students in 5^{th} – 12^{th} grade reported using marijuana, which is above that of the national rate (Fregoso et al., 2015).

Conclusions

The current report is a comprehensive review of marijuana to include its history, composition, methods of consumption, therapeutic effects and health consequences, legislation, and the impact of marijuana in the Paso Del Norte region with author's recommendations on decategorization, further research, and additional education among healthcare professionals regarding marijuana. Records indicate that marijuana has been used for medicinal purposes for thousands of years. Marijuana contains over 400 chemicals and approximately 104 of these chemicals are cannabinoids (ElSohly and Gul, 2014). There are numerous products created that include cannabinoids (e.g., THC and CBD) with various forms of consumption (e.g., edibles, topicals). Multiple studies support using marijuana or cannabis-based medications for therapeutic effects, however, there are mixed opinions when addressing the health consequences. Legalization in some states have resulted in treatment for substance abuse, reduction in prescription medications, and mixed results on crime.

Arguably, tobacco and alcohol comprise no medicinal benefits and are associated with high fatality rates due to addiction and use-related illnesses, yet each substance is legal to consume at a given age (i.e., age $\geq$ 18 years; age $\geq$ 21 years; respectively). In contrast, marijuana is not associated with high fatality rates due to addiction and use-related illnesses, yet marijuana is illegal to consume in non-legal marijuana states. Furthermore, "no one has died from an overdose of cannabis" (Sifferlin, 2017). A problem that is discussed in many states that have legalized marijuana is that the arrests due to marijuana possession impact people's lives permanently. For example, more than 200,000 American students have lost federal financial aid eligibility because of a drug conviction (e.g., possession of marijuana) (Drug Policy Alliance, 2018b). "*Stop ruining people's lives for marijuana*" was the promise that was proposed in

Proposition 64, the initiative that legalized recreational marijuana use in California in 2016 (Proposition 64, 2016). Moreover, a topic that is increasingly discussed relates to evidence that has surfaced suggesting that there are disproportionate mass incarcerations of minority drug offenders (Golub, Johnson, & Dunlap, 2007; Alexander, 2012). For example, smoking marijuana in public view is the most common misdemeanor arrest in New York City and most of the arrestees are either black or Hispanic (Golub, Johnson, & Dunlap, 2007). Notably, in comparison to whites, the black and Hispanic arrestees were more likely to be detained prior to an arraignment, convicted, and sentenced to jail (Golub, Johnson, & Dunlap, 2007). An article published in the New York Times on May 13th, 2018 highlighted these findings with a headline that read, "*Surest Way to Face Marijuana Charges in New York: Be Black or Hispanic*" (Mueller, Gebeloff, & Chinoy, 2018).

Given the current scientific evidence regarding the therapeutic effects and health consequences associated with marijuana use, the authors of the current review support the de-categorization of marijuana as a Schedule I drug. We recommend the change to support additional research and assessment of the impact that medicinal marijuana could have on wellbeing and quality of life. In contrast, we believe that further research is needed to make a decision regarding supporting or opposing the legalization of recreational marijuana. We acknowledge that there is a problem related to the amount of incarcerations associated with marijuana possession in states in which marijuana is not legal. The authors of the current review suggest that discussions regarding the decriminalization of marijuana (e.g., reducing penalties associated with the possession of small amounts of marijuana for personal use and removing a permanent criminal record) are warranted while further research is conducted to properly evaluate the benefits and consequences of legalizing medicinal and/or recreational marijuana.

Considering the evidence regarding disproportionate mass incarcerations of minority drug offenders, decriminalizing marijuana could have an impact on the Paso Del Norte region, comprised of a Hispanic majority population (Healthy Paso Del Norte, 2018).

Overall, we conclude that medical marijuana could be an appropriate treatment for illnesses that marijuana has been shown to produce positive outcomes, *especially* in cases in which the patient is resistant to other treatments. In contrast, legalization of recreational marijuana needs to be supported by strong policies and effective mechanisms to monitor use and the social, economic, and health impact. Given the national trend toward the legalization of both medicinal and recreational marijuana, we believe that health professionals will increasingly be consulted by patients regarding the use of marijuana as a treatment. Thus, we advocate that there is a need for formal education on marijuana within school curriculums so that health professionals are prepared to address many of the questions and concerns associated with using marijuana as a treatment. Moeller and Woods (2015) reported that pharmacy students receive minimal "formal" education on marijuana. Specifically, the authors recruited 311 pharmacy students to complete a survey assessing attitudes and knowledge about marijuana and its associated therapeutic effects and health consequences. More than half (58%) of students reported that they believed medical marijuana should be legalized in all states, however, the majority of students did not feel comfortable answering consumer questions related to marijuana including the efficacy, safety, and drug interactions associated with using marijuana. In addition, the authors reported that there was low accuracy in responses for diseases and conditions that medical marijuana could be prescribed to treat.

Many gaps in knowledge emerged while conducting this review. For example, future research should investigate the fluctuations in CBD or THC content in extracts and edibles with

aims of improving the accuracy of doses on product labels. These fluctuations in the content of CBD or THC could lead to inaccurate estimates of proper dosing and unintentional intoxications. Another gap in the literature is that research findings related to marijuana users includes subjects who are poly-users (e.g., use tobacco and / or alcohol in addition to marijuana). Future studies need to exclude poly-users in order to better understand "marijuana-only" effects. Additionally, as more states begin to legalize marijuana, the number of adults who will drive after consuming legal amounts of marijuana in combination with legal amounts of alcohol are likely to rise. Future research needs to investigate methods for regulating driving under the influence of marijuana and alcohol in combination, as research suggests that driving performance is detrimentally impacted by the simultaneous use of each substance. Research is also warranted on regional data to include marijuana use, marijuana legislation support, perceived risk of marijuana, intentions to use, and intention to use if legalized. Lastly, it is important to analyze and better understand the psycho-social and physical health, crime and legal ramifications, and economic repercussions that marijuana legalization would have in the Paso del Norte region.

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Table 1.
31 U.S. jurisdictions with medical marijuana laws as of December 03, 2018.

Jurisdiction	Medical Marijuana Year Passed	Recreational Marijuana Year Passed
1. Alaska	1998	2014
2. Arizona	2010	
3. Arkansas	2016	
4. California	1996	2016
5. Colorado	2000	2012
6. Connecticut	2012	
7. Delaware	2011	
8. Florida	2016	
9. Hawaii	2000	
10. Illinois	2013	
11. Louisiana	2016	
12. Maine	1999	2016
13. Maryland	2014	
14. Massachusetts	2012	2016
15. Michigan	2008	
16. Minnesota	2014	
17. Missouri	2018	
18. Montana	2004	

19. Nevada	2000	2016
20. New Hampshire	2013	
21. New Jersey	2010	
22. New Mexico	2007	
23. New York	2014	
24. North Dakota	2016	
25.Ohio	2016	
26. Oklahoma	2018	
27. Oregon	1998	2015
28. Pennsylvania	2016	
29. Rhode Island	2006	
30. Utah	2018	
31. Vermont	2004	2018
32.Washington	1998	2012
Washington, DC	2010	2014
33.West Virginia	2017	

Note: The information presented was compiled from ProCon.org (2018).

Table 2.
Various Methods of Consuming Marijuana

Brief Description	Product Description
Smoking marijuana is the most common method of consumption. Involves applying a flame to burn the dry leaves of marijuana and inhaling the smoke.	**Pipe:** Glass, wood, or metal device that marijuana can be inserted into and used to inhale smoke. **Bong or bubbler:** Glass or plastic device that uses water-filtration to filter smoke prior to entering the lungs. **Dab:** Concentrated oil that is extracted using a solvent such as butane or carbon dioxide. A flame is applied to the oil and the smoke is inhaled. **Joint:** Unfiltered cigarette filled with marijuana. **Blunt:** Cigar filled with marijuana.
Vaporizing marijuana is an emerging method of consuming marijuana and involves heating dry cannabis leaves or concentrated THC/CBD oil to a level high enough to transmit the THC/CBD without the full combustion that results in smoke. Vaporizing marijuana has gained popularity because it is believed to be a healthier option for consuming marijuana without emitting the carcinogens, tars, and toxins from combusted smoke.	**Desktop Vaporizer:** Device that connects to an electrical wall outlet and allows for the temperature of the heating device to be adjusted precisely. **Portable Vaporizer:** A battery operated device that allows for mobile use. THC /CBD oils can be combined with flavors (e.g., cherry) to provide a pleasant taste and aroma to the vapor that is inhaled and exhaled. E-cigarettes are becoming the most common portable vaporizer due to their sleek size and discreet appearance.
Ingesting marijuana edibles involves extracting THC/CBD from the dry leaves of cannabis and creating a butter that can be used for cooking or baking.	**Candy:** Examples of THC/CBD infused candy include lollipops, gummy bears, and chocolates. **Baked Goods:** Common baked goods include brownies, cookies, and cupcakes. However, it is important to note that marijuana infused butter can be used to cook/bake any food or snack that includes butter as an ingredient.
Ingesting marijuana beverages are growing in popularity because they are easier to uptake into the intestines and have lower fat content than edibles (i.e., brownies).	**Coffee, Hot Coco, Tea, Alcohol, Soda:** Beverage is infused with marijuana.

Other marijuana pharmacological derivatives: capsules, spray, tinctures, and topicals are designed to be absorbed orally or through one's skin.	**Capsule:** Cannabis extract of THC/CBD inserted into a capsule to be consumed orally. **Spray:** Concentrated CBD cannabis extract that is applied to specific area of body and absorbed through one's skin. **Tincture:** Concentrated THC or CBD cannabis extract that is applied to specific area of body and absorbed through one's skin.

Table 3.
Conclusive or Substantial Evidence Provided by the National Academies of Sciences, Engineering, and Medicine (2017) Committee

Cannabis or cannabinoids are effective for treating:
Chronic Pain: Significant reduction in pain symptoms (cannabis)
Chemotherapy-induced vomiting: Oral cannabinoids are effective antiemetics (oral cannabinoids)
Multiple Sclerosis Spasticity Symptoms: Improves "patient-reported" spasticity symptoms (oral cannabinoids)

Table 4.
Moderate Evidence of Effectiveness Provided by the National Academies of Sciences, Engineering, and Medicine (2017) Committee

Cannabis or cannabinoids are effective for treating:
Sleeping Aid: Improves short-term sleep outcomes associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, nabiximols[1])

Table 5.
Limited Evidence of Effectiveness Provided by the National Academies of Sciences, Engineering, and Medicine (2017) Committee

Cannabis or cannabinoids are effective for treating:
HIV/AIDS: Increases appetite and decreases weight loss associated with HIV/AIDS (cannabis and oral cannabinoids)
Multiple Sclerosis Spasticity Symptoms: Improves "clinician-measured" spasticity symptoms (oral cannabinoids)
Tourette Syndrome: Improves symptoms associated with Tourette's (e.g., reduction in tics) (THC Capsules)
Social Anxiety Disorder (SAD): Improves anxiety symptoms (cannabidiol)
Posttraumatic Stress Disorder (PTSD): Improves global clinical state, general well-being, and reduces nightmares (Naboline[2])

Table 6.
Limited Evidence of a Statistical Association Provided by the National Academies of Sciences, Engineering, and Medicine (2017) Committee

Cannabis or cannabinoids are effective for treating:
Traumatic Brain Injury or Intracranial Hemorrhage: Improves overall outcomes such as reduction in mortality or disability (Cannabis)

Table 7.
Limited Evidence of Ineffectiveness Provided by the National Academies of Sciences, Engineering, and Medicine (2017) Committee

Cannabis or cannabinoids are ineffective for treating:
Dementia: Increases weight gain, decreases disturbed behavior, and decreases negative affect scores (cannabinoids)
Glaucoma: Improves intraocular pressure (cannabinoids)
Chronic Pain or Multiple Sclerosis Depressive Symptoms: Reduces depressive symptoms (nabiximols, dronabinol, nabilone)

Table 8.
Insufficient or No Evidence Provided by the National Academies of Sciences, Engineering, and Medicine (2017) Committee

Cannabis or cannabinoids are effective for treating:
Cancers: Anti-tumor effects (cannabinoids)
Cancer-Associated Anorexia Cachexia Syndrome and Anorexia Nervosa: Increases in weight (cannabinoids)
Irritable Bowel Syndrome: Improves gastric transit, small bowel transit, or colonic transit (dronabinol)
Epilepsy: Reduction in seizure frequency (cannabinoids)
Spinal Cord Injury Spasticity in Paralyzed Patients: Reduction in muscle spasticity (cannabinoids)
Amyotrophic Lateral Sclerosis: Increases in appetite and sleep, decreases in cramps or fasciculations (involuntary muscle twitches) (cannabinoids)
Huntington's Disease: Decreases in chorea (abnormal, involuntary movements), decline in cognitive abilities, psychiatric impairment (oral cannabinoids)
Parkinson's Disease or Levodopa-Induced Dyskinesia: Improvements in dyskinesia (abnormal, involuntary movements), quality of life, sleep, or pain (cannabinoids)
Dystonia: Reduction in dystonia as indexed by the Burke-Fahn-Marsden dystonia scale (naboline or dronabinol)
Addictive Substances: Abstinence from addictive drugs including marijuana (cannabinoids)
Schizophrenia or Schizophreniform Psychosis Mental Health Outcomes: (cannabidiol)

Table 9.
Research Published After the NASEM (2017) Committee Review Regarding the Therapeutic Effects of Marijuana

Affliction Described in National Academies of Sciences, Engineering, and Medicine (2017)	Updated Research
Chronic Pain:	A literature review by Park and Wu (2017) examined 25 articles that assessed prevalence of medical marijuana use, reasons for using medical marijuana, and the perceived effects of medical marijuana. The authors concluded that the most commonly endorsed self-reported reason for using medical marijuana was to mitigate pain. Fanelli et al. in 2017 recruited 614 adults in Italy to assess the effectiveness of cannabis to treat chronic pain from various diseases (e.g. multiple sclerosis, cachexia and anorexia among AIDS and cancer patients, glaucoma, Tourette syndrome, and certain types of epilepsy). Participants were given various doses and strains of cannabis for the treatment of chronic pain. The treatment was given alongside their regular prescribed treatment and self-reported data was collected to assess levels of pain. The authors concluded that cannabinoids appear to be an effective and safe method for treating chronic pain. Savage et al. in 2016 reviewed the clinical and policy literature related to marijuana use for the treatment of pain. The article included information for healthcare professionals on protocols for the use of marijuana with their patients. The review concludes that there are promising results for the use of marijuana for pain. This review is useful for researchers and healthcare professionals as it highlights clinical practice and future research. Boehnke et al. in 2016 conducted a cross-sectional retrospective survey of 244 medical marijuana patients with chronic pain who obtained medical marijuana from a Michigan dispensary from November 2013 to February 2015. The article found that marijuana use was associated with lower opioid use, increased quality of life and fewer medication side effects among chronic pain patients. The study reports that marijuana use is effective for treating chronic pain, however, an important caveat to consider relates to the potential synergistic effects of using marijuana and opioids concurrently. Haroutounian (2016) recruited 176 participants (≥ age18) that had experienced chronic pain lasting at least 3 months and previous adverse

	effects from 2 different drug classes at full dosage. The objective of this study was to determine long-term effects of medical marijuana on pain in participants with treatment-resistant chronic pain. S-TOPS pain score improved from 83.3 to 75.0 and pain symptom score improved in 65% of participants. Findings suggests that cannabis treatment in mixed groups of patients with treatment resistant chronic pain can result in better quality of sleep, improved pain management, and a reduction of the use of opioids.
Chemotherapy-Induced Vomiting:	Badowski (2017) conducted a pub med search to identify articles related to cannabinoids and the treatment of nausea due to chemotherapy. The purpose of this review was to provide a summary of the efficacy, pharmokinetics, pharmodynamics and safety of cannabinoids for patients with chemotherapy-induced vomiting. Oral cannabinoids improved efficacy or had similar results as conventional antiemetics in treating patients with chemotherapy induced vomiting. The authors concluded that oral cannabinoids are effective at managing nausea and vomiting that is induced from chemotherapy but can have adverse effects when compared to medication normally used to treat similar symptoms (e.g., dizziness).
Multiple Sclerosis Spasticity Symptoms:	Gyang Hyland, Samkoff, and Goodman (2018) conducted a cross sectional study among patients that had been diagnosed with multiple sclerosis (MS) and transverse myelitis (TM). Fourteen subjects were recruited from the University of Rochester MS Center and thirteen of the subjects reported that they have used medicinal marijuana and 62% reported that they use marijuana daily. The objective of this study was to determine the effectiveness of medical marijuana in the management of symptoms of MS and TM. Approximately 77% of the sample reported that medical marijuana improved their quality of life. Additionally, the subjects that reported that marijuana improved their quality of life also reported that marijuana was useful for managing symptoms and did not cause any side effects. The authors concluded that medical marijuana seems to play a significant role in managing symptoms from MS and TM by reducing spastic pain and by reducing the need to take other medications. van Amerogen et al. (2017) conducted a two-phase study in patients with multiple sclerosis (MS). The goal of this study was to determine the effectiveness of THC in reducing spasticity in patients with MS. Biomarkers were used to study secondary pharmodynamic effects and efficacy of the treatments with THC. Immediately after administration of THC, pain was reported to have been reduced significantly by patients. The authors concluded that oral use of THC for reducing the pain in spastic patients with MS seems to be efficacious and may play a role in the treatment of MS altogether due to the stable pharmacokinetic profile of THC.

	Patti et al., (2016) recruited a MS patient population of 1615 subjects from 30 MS centers across Italy who were taking the oromucosal spray, Sativex®. The researchers aimed to describe the effectiveness and adverse events of Sativex®. Researchers wanted to determine how effective the spray would be for treatment-resistant multiple sclerosis (MS). Adverse effects as a result of taking the spray were also recorded. After one treatment month, 70.5% of the subjects reached a ≥ 20% improvement (initial response, IR) and 28.2% of the subjects reached a ≥ 30% improvement (clinically relevant response, CRR) with a mean NRS score reduction of 22.6. Importantly, during the 6 months of treatment, 39.5% of the subjects discontinued treatment for a number of reasons including lack of effectiveness or adverse events. The study concluded that Sativex® could be considered a useful and safe option for patients with MS that experience moderate to severe spasticity.
Sleeping Aid: **[Opposite effect]**	Conroy et al. (2016) recruited 98 participants and examined associations between marijuana use and sleep patterns. The objective of this study was to determine the difference in the effects marijuana has on sleep with users that consume at different rates (daily vs. non-daily users). Quality of sleep and sleep patterns of the participants were also investigated. The authors assessed dependence for marijuana use over the 4 weeks preceding the survey and smokers were categorized as either daily smokers (smoke marijuana at least 6 days per week), non-daily smokers (smoke marijuana at least once per month, up to 5 days per week), and non-users (no marijuana use in the past month). Sleep disturbance was reported at 55.1% in daily marijuana users, 34.5% in non-daily users, and 45% of non-users. This study also gathered the rates of clinical insomnia in daily users (38.8%), non-daily users (10.3%), and non-users (20.0%). Daily marijuana users were found to experience more sleep disturbances than non-daily users. Non-daily users and non-users both had similar measures. This study suggests that daily marijuana use may not improve sleep. Studies with larger numbers of participants are warranted.
HIV/AIDS: **[No effect]**	Sinha et al. (2017) conducted a cohort study with patients enrolled in Johns Hopkins HIV Clinic. A total of 1377 participants that were receiving anti-viral therapy were selected to participate in study. The study focused on the relationship between marijuana use and HIV treatment without alcohol or other drug use. The results suggest that there is not a statistically significant relationship between marijuana use and treatment outcomes. In addition, marijuana use frequency was not associated with negative treatment outcomes.
Tourette Syndrome:	Abi-Jaoude (2017) identified 19 patients with Tourette Syndrome (TS) at a western Toronto clinic. Participants were included in the study if they were diagnosed with TS and used marijuana regularly for 6 months or longer. The goal of this study was to determine the effectiveness and tolerability of marijuana treatments in adult patients with TS. All participants in the study experienced significant symptom relief. Importantly, 18 of the 19 participants described the results of using

	marijuana to treat TS as "much improved". Tic scores also decreased by 60% in patients. The authors reported that marijuana was well tolerated by participants and appears to be a good option for treating patients with TS with tic associated symptoms. While success was found in treating TS patients with marijuana, it is important to note patients continued to take other medications concurrently.
Social Anxiety Disorder (SAD):	*No new studies identified using the mentioned search criteria.*
Posttraumatic Stress Disorder (PTSD):	*No new studies identified using the mentioned search criteria.*
Traumatic Brain Injury or Intracranial Hemorrhage:	*No new studies identified using the mentioned search criteria.*
Dementia:	*No new studies identified using the mentioned search criteria*.
Glaucoma:	*No new studies identified using the mentioned search criteria.*
Chronic Pain or Multiple Sclerosis Depressive Symptoms:	*No new studies identified using the mentioned search criteria.*
Cancers:	Bogdanovic (2017) conducted a literature survey of medical and scientific databases with a focus on cannabinoids in cancer treatment. The aim of the review was to discuss and overview the most significant findings concerning cannabinoids in potential cancer treatment. Through cannabinoid receptor and non-receptor signaling pathways, cannabinoids demonstrate specific cytotoxicity against tumor cells, while protecting healthy tissue from apoptosis. Cannabinoids also display potent anticancer activity against tumor xenografts, including tumors that express high resistance to standard chemotherapeutics. These findings suggest cannabinoids have the potential to aid in cancer treatment, more specifically anti-tumor effects. While these findings are promising, it is important to note that few clinical trials that study the effects of cannabinoids on cancers in human patients have been conducted. Further research on the subject are warranted.
Cancer-Associated Anorexia Cachexia Syndrome and Anorexia Nervosa:	*No new studies identified using the mentioned search criteria.*
Irritable Bowel Syndrome:	*No new studies identified using the mentioned search criteria.*
Epilepsy:	Devinsky et al., (2018) conducted an open label trial with patients that were 30 years of age or younger. The objective of the study was to

	determine the effects CBD (Epidiolex) treatment would have on patients with epilepsy, CDKL5 deficiency disorder, Aicardi, Doose, and, Dup15q. All of the patients in the study had a case of severe childhood–onset epilepsy. The study included 55 patients of which 20 had CDKL5 disorder, 19 had Aicardi syndrome, 8 with Dup15q syndrome, and 8 with Doose syndrome. Patients received 10 or more weeks of CBD treatment as part of a prospective interventional study. All patients who used CBD were found to have decreased seizure frequencies when compared to baseline reports. At baseline, patients (n=46) were found to have a seizure frequency rate of 59.4%. At week 12 of the study patients (n=35) had a seizure frequency rate of 22.5% and at 48 weeks patients (n=27) seizure frequency rates were at 23.3%. This study provides valuable data and evidence of long-term efficacy of the treatment of epilepsy, CDKL5 deficiency disorder, Aicardi, Dup15q, and Doose syndromes with CBD (Epidiolex). The study suggested that future research should aim at including placebo- controlled randomized trials to further address concerns for safety in using CBD to treat patients with epilepsy. Rosenberg, Louik, Conway, Devinsky, and Friedman (2017) conducted a study that included 48 patients between the ages of 1-30 years old that reported to currently have or previously had intractable childhood onset epilepsy. Patients also reported having 4 or more seizures with a motor component per 4-week period. After enrollment into the study, patients kept a daily diary over a 4-week period to generate a baseline report on daily seizures. A quality of life in childhood epilepsy survey was also included to assess multiple quality of life domains. The objective of the study was to determine the potential seizure reducing properties of Epidiolex, which is purified CBD. Monthly motor seizure frequency was 27.5% at baseline, however, by the 12-week observation period of the study the monthly motor seizure frequency reduced to 13.9%. Quality of life survey scores also increased after the 12 weeks of treatment. Specifically, survey scores were at 37.8% at baseline; following the 12 weeks of treatment survey scores had improved to 45.7%. The results of this study suggest that the effects of CBD on patients with epilepsy could extend further than just reducing seizure frequencies and also improve the overall quality of life in these patients. However, the authors suggest that further studies utilizing placebo controlled, double-blind trials are needed to confirm this claim. O'Connell, Gloss, and Devinsky (2017) conducted a literature review examining the use of cannabinoids on patients with treatment-resistant epilepsy. Open label studies and randomized control trials were included within the review. The goal was to determine the safety and efficacy of the drug Epidiolex for the treatment of seizures when compared to a placebo. The authors reported that in a sample of 120 patients with Dravet Syndrome who had been taking at least 3 anti-epileptic drugs

	were assessed. The baseline rates for median convulsive seizure frequency was 13 per month. Sixty-one patients received Epidiolex 20 mg/kg per day and 59 received the placebo. After the 14-week treatment period had concluded, researchers determined that the median reduction of epileptic seizures was 39% in the Epidiolex group and 13% in the placebo. Although CBD may be effective at reducing convulsive seizures in patients with epilepsy, the safety and efficacy of THC when used alone or with CBD is still undefined in children and adults with any epilepsy syndrome. Randomized control trials are necessary to properly determine the safety and efficacy of THC. Devinsky et al., (2016) conducted an open label trial that involved patients between the ages of 1-30 years of age who were diagnosed with severe, intractable, childhood-onset, treatment resistant epilepsy. The main objective of this study was to determine the safety and tolerability of cannabidiol and its effects on the mean frequency of motor seizures at 12 weeks. Patients were given a dose of oral cannabidiol that ranged from 2-5mg/kg per day. Dosage was up-titrated until the cannabidiol could no longer be tolerated or until the dosage of 25 mg/kg or 50mg/kg per day depending on the study site. At baseline the median monthly frequency of motor seizures was 30.0 (IQR 11·0–96·0) and reduced to 15.8 (5·6–57·6) after 12 weeks of treatment. The median reduction in monthly motor seizures was 36.5% (IQR 0–64·7). This study's findings suggest that cannabidiol reduces the frequency of seizures and may have a safety profile good enough for its use in children and young adults that have been diagnosed with treatment-resistant epilepsy. Further studies that make use of randomized controlled trials of the use of cannabidiol are warranted to further understand the safety profile and efficacy of its use. Tzadok et al., (2016) examined the efficacy of treatment with cannabis oil to in young children and adolescents ages 1-18 that were diagnosed with epilepsy. Seventy-four patients who were resistant to more than 7 antiepileptic drugs were recruited and treated for at least 3 months with cannabis oil. Nearly 9 out of 10 (89%) patients reported reductions in seizure activity. Thirteen patients (17.57%) reported 75-100% reduction in seizure activity, 25 (33.78%) patients reported a 50-75% reduction in seizure activity, nine (12.16%) patients reported a 25-50% reduction in seizure activity, and 19 (25.68%) reported less than 25% reduction in seizure activity. The authors suggest that cannabis oil is an effective treatment against seizures for children with epilepsy and further studies using cannabis oils are needed to replicate these findings.
Spinal Cord Injury Spasticity in Paralyzed Patients:	*No new studies identified using the mentioned search criteria.*

Amyotrophic Lateral Sclerosis:	*No new studies identified using the mentioned search criteria.*
Huntington's Disease:	Saft (2018) studied 7 patients with Huntington's disease (HD) with significant chorea and dystonia. Chorea and dystonia subscores were taken before and after the administration of cannabinoids to determine if cannabinoids can help motor symptoms in patients with HD. Motor score and dystonia subscore improved from 70.9 to 60.6 with a mean difference of 10.3 and from 12.3 to 8.0 with a mean difference of 4.3. Cannabinoids improved motor symptoms, provided patients with healthy weight gain and reduced apathy and irritability in patients.
Parkinson's Disease or Levodopa-Induced Dyskinesia:	*No new studies identified using the mentioned search criteria.*
Dystonia:	*No new studies identified using the mentioned search criteria.*
Addictive Substances:	*No new studies identified using the mentioned search criteria.*
Schizophrenia or Schizophreniform Psychosis Mental Health Outcomes: **[No effect]**	Boggs et al., (2018) used a randomized placebo controlled and a parallel group who had a fixed dose of oral CBD. The researchers used 36 stale antipsychotic-treated patients diagnosed with chronic schizophrenia and compared the cognitive, symptomatic and side effects of CBD versus a placebo in clinical trial. They used MATRICS Consensus Cognitive Battery (MCCB) and the Positive and Negative Syndrome Scale (PANSS) as measures for testing. CBD augmentation was not associated with an improvement in MCCB or PANSS scores and CBD was well tolerated without worsening of mood, suicidality, or movement side effects. These findings in this study are important because in this particular case CBD augmentations did not provide benefits or negative consequences.

Note: Table adapted from the National Academies of Sciences, Engineering, and Medicine (2017) report titled: "*The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research"*.

Table 10.
Summary of the Health Problems Associated with Smoking Marijuana According to NASEM (2017)

	Substantial Evidence	Moderate Evidence	Limited Evidence	No or Insufficient Evidence	Updated Research
Cancer		No statistical association that smoking marijuana increases incidence of lung cancer, or head cancer and neck cancers.	Non-seminoma-type testicular germ cell tumors.	Esophageal cancer, prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, or bladder cancer **Parental use and risk of development of cancer in offspring:** acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lympoblastic, leukemia, rhabdomyosarcoma, astroctyma, or neuroblastoma.	*No new studies identified using the mentioned search criteria.*
Cardiometabolic Risk			Acute myocardial infarction, ischemic stroke or subarachnoid hemorrhage,	Myocardial infarction.	*No new studies identified using the mentioned search criteria.*

			decreased risk of metabolic syndrome and diabetes, increased risk of prediabetes.		
Respiratory Disease	Worse respiratory symptoms and increased chronic bronchitis episodes.	Improved airway dynamics with acute use, but not chronic use; higher forced vital capacity; improvements in respiratory symptoms.	Chronic obstructive pulmonary disease (COPD) when controlled with tobacco use.	Hospital admissions for COPD; asthma development or exacerbation.	*No new studies identified using the mentioned search criteria.*
Immunity			Decrease in production of several inflammatory cytokines. No statistical association with progression of liver fibrosis or hepatic disease in viral Hepatitis C patients.	Adverse immune cell responses in healthy individuals. Adverse effects on immune systems of HIV patients. Increase in oral human papilloma virus (HPV).	Keen et al. (2017) gathered individuals who tested negative for THC (n=70) and individuals who tested positive for THC (n=25). All 95 of the participants were African American and tested positive for HIV. The objectives of this study was to determine the effects of marijuana use with people that tested positive for HIV. Patients who

					tested positive for THC had higher CD4+ and CD8+ lymphocyte counts than those who did not consume THC. These findings suggest that THC does not reduce immune function measured by CD count. This study echoes the results of other studies and also suggests that marijuana may interfere with the virus' ability to transfer from one cell to the next.
Injury and Death	Risk of motor vehicle crash.	Risk of overdose injuries (i.e., respiratory distress) in pediatric populations.		Occupational accidents or injuries, death due to overdose.	*No new studies identified using the mentioned search criteria.*
Prenatal, Perinatal, and Neonatal Exposure **(Maternal Outcomes included)**	Lower birthrate in offspring.		Pregnancy complications or admissions of infant to neonatal intensive care unit (NICU).	Offspring outcomes: cognition/academic achievement, sudden infant death syndrome, or later substance use.	Gunn et al. (2016) conducted a meta-analysis examining maternal and child health outcomes associated with prenatal exposure to cannabis and

					reported that anaemia is the "*most widely discussed maternal outcome in cannabis-pregnancy literature.*" Specifically, the odds of women who used marijuana during pregnancy and developed anaemia increased significantly (pooled OR = 1.36, 95% CI = 1.10 to 1.69) compared to women who did not use marijuana during pregnancy. An important caveat highlighted by the authors is that most research on marijuana users involves concurrent users of tobacco and marijuana, thus ruling out a marijuana-only

					effect is often challenging.
Psychosocial		Impairment in cognitive domains of learning, memory, and attention.	Impaired academic achievement and education outcomes; impaired social functioning; increased rates of unemployment or low income.	Sustained abstinence from using marijuana and impairments the following cognitive domains: learning, memory, and attention.	Meier, Caspi, Danese, Fisher, Houts, Arseneault, & Moffitt, (2018) examined 1989 twins from the Environmental Risk (E-Risk) Longitudinal Twin Study. Specifically, the authors examined the impact of frequency of marijuana use and marijuana dependence on neuropsychological decline as indexed by intelligence quotient (IQ) scores. The authors found that twin who used marijuana more frequently than their co-twin did not score differently on 5-6 executive function tests (*P*s > 0.10).

					The authors concluded that short-term marijuana use in adolescents does not cause a decline in IQ or impair executive functions. Notably, the authors explain that even when marijuana use reaches the level of dependence, there is still not a decline in IQ or executive functions. The authors claim that family background factors are the causal factor explaining why adolescent marijuana users typically perform worse on IQ or executive function tests that non-users. Hirst, Young, Sodos, Wickham, and Earleywine

					(2017) recruited 62 participants that were chronic cannabis users and asked them to complete a neuropsychological battery which included the California Verbal Learning Test-II. The objectives of this study was to determine if effort had an effect on frequency or age of long term cannabis use and learning/memory performance. Participants who used cannabis more frequently than others displayed poorer effort measured by the world memory test. This study's findings indicate that effort is the driving force between the frequency of

					cannabis use and performance on learning and memory measures.
Mental Health	Frequency of use associated with development of schizophrenia or other psychoses.	Increased suicidal ideation, attempts, and suicide completion; increased incidence of social anxiety disorder; slight increased risk for the development of depressive disorders. **Individuals diagnosed with psychotic disorders experience:** improved cognitive performance. **Individuals diagnosed with bipolar disorder experience:** increased mania and hypomania symptoms. **Individuals with psychotic disorders:** No	Increase in symptoms of anxiety; increase in developing bipolar disorder and anxiety disorders. **Individuals with psychotic disorders:** Increase in positive symptoms of schizophrenia. **Individuals with posttraumatic stress disorder (PTSD)** Increased severity of PTSD symptoms.	Changes depressive disorder symptoms or the development of PTSD.	*No new studies identified using the mentioned search criteria.*

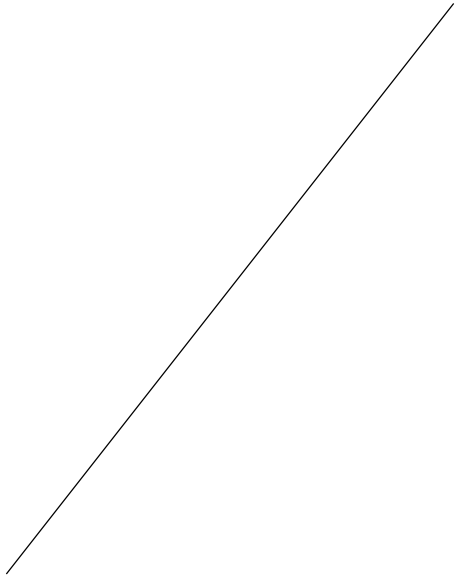
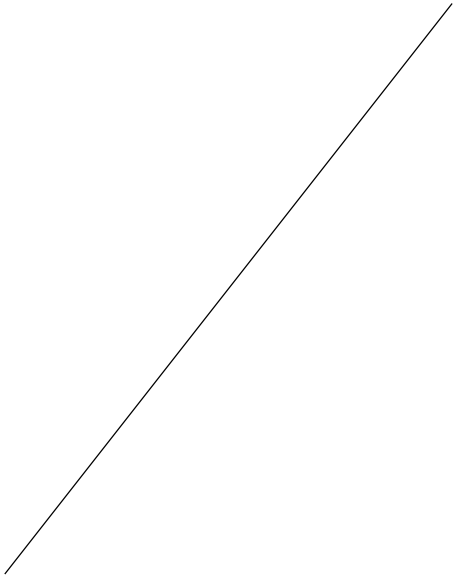
		statistical association of worsening negative symptoms of schizophrenia.			
Problem Marijuana Use	Frequency of use is associated with developing problematic marijuana use. **Risk factors for developing problematic marijuana use:** initiating marijuana use at early age, being a male cigarette user. Attention deficit hyperactivity disorder (ADHD) being treated with stimulants does not result in problematic cannabis use.	History of psychiatric treatment; increased severity of PTSD symptoms. **Risk factors for developing problematic marijuana use:** being a male, having major depressive disorder, combined use of abused drugs. **Risk factors for developing problematic marijuana use in adolescents:** Frequency of use, poor school performance, antisocial behaviors, childhood sexual abuse, initiation of alcohol at early age, exposure of	Childhood anxiety and childhood depression.		Guttmannova et al. (2017) recruited 808 participants who regularly consumed marijuana during adolescence and young adulthood. The objectives of this study was to explore the relationship between regular marijuana use from adolescence to adulthood and its effect on the mental health of participants at age 33. Regular marijuana use from adolescence to adulthood was positively associated with cannabis use disorder, alcohol use disorder, and nicotine

		combined used of abused drugs. **Not risk factors for developing problematic marijuana use in adolescents:** Adolescent ADHD; anxiety, personality disorders, and bipolar disorders; alcohol dependence; nicotine dependence.			dependence at age 33.
Abuse of Other Substances		Development of substance dependence or substance abuse disorder for alcohol, tobacco, and other illicit drugs.	Initiation of tobacco use; changes use patterns of licit and illicit substances.		*No new studies identified using the mentioned search criteria.*

Appendix A

Law Descriptions in PdN Region

	Mexico	New Mexico	Texas	Federal
Description	Congress approved medical use marijuana and its pharmaceutical derivatives.	New Mexico became 12th state to allow medical cannabis with the Lynn and Erin Compassionate Use Act. The purpose is to allow the beneficial use of medical cannabis in a regulated system for alleviating symptoms caused by debilitating medical conditions (i.e., cancer, glaucoma, multiple sclerosis, damage to the nervous tissue of the spinal cord, epilepsy, HIV, admitted to hospice care, & others approved by the department of health) and their medical treatments.	The Texas Compassionate Use Act was enacted to allow patients with intractable epilepsy to access low-THC cannabis. The bill required the Texas Department of Public Safety (DPS) to create a secure registry of physicians who treat epilepsy. DPS licensed 3 dispensing organizations that meet requirements. The license authorizes the organizations to cultivate, process, and dispense low THC cannabis to prescribed patients.	The use, sale, and possession of all forms of cannabis in the United States is illegal under federal law. As a Schedule I drug under the federal Controlled Substances Act of 1970, cannabis is considered to have "no accepted medical use" and have a high potential for abuse and physical or psychological dependence. Individual states have enacted legislation permitting exemptions mainly for medical and industry use.
Adoption Year	2017	2007	2015	1970
Bill	Articulo 237	Senate Bill 523	Senate Bill 339	Controlled Substances Act

Requirements	Products that contain derivatives of cannabis in concentrations of 1% or less of THC.	A patient can apply by completing an application. Application includes: patient's information and signature; signature from provider with prescribing authority certifying the applicant has been diagnosed with one of the qualifying conditions. A valid New Mexico ID. A practitioner needs to be licensed in NM to prescribe and administer drugs that are subject the Controlled Substances Act.	Patient must be a permanent resident of Texas, diagnosed with intractable epilepsy, qualified physician determines medical use and second qualified physician concurs. Physician must enroll in the Compassionate Registry of Texas (CURT) System. Dispensing organization must be approved by DPS.	
Enrollment	Ministry of Health (La Secretaría de Salud) is responsible for development and enforcement of public policies to regulate the medical use. * as per website – no updates due to federal elections (July 2018)	Application is reviewed medically and administratively to ensure all requirements are met. Possession of no more than 230 units (~8 oz) over a 3 month period. The right to purchase from a Licensed Non-Profit Producer. The right to posses any paraphernalia in connection with their use of medical cannabis. If the patient is not in possession of their card, they shall be given time to produce card before arrest or criminal charges. The right to	The 3 dispensing organization licenses are to Cansortium Texas, Compassionate Cultivation, and Surterra Texas; DPS not accepting applications for new enrollees. Low-THC cannabis is defined as marijuana that contains 10% or more cannabidiol (CBD) and not more than 0.5% tetrahydrocannabinol.	

		apply for a personal production licenses (PPL), to allow enrollee to grow for personal use. If approved, patient can have up to 16 plans, 4 mature (flowering), and 12 seedlings.		
Restrictions		Criminal prosecution or civil penalty for possession, distribution, transfer, or use of cannabis or a cannabis-derived product (1) in a school bus or public vehicle; (2) on school grounds or property; (3) in the workplace of the qualified patient's or primary caregiver's employment; (4) at a public park, recreation center, youth center, or other public place; (5) to a person not approved by the department pursuant to this rule; (6) outside New Mexico or attempts to obtain or transport cannabis, or cannabis-derived products from outside New Mexico; or (7)that exceeds the allotted amount of usable medical cannabis, or cannabis-derived products.	Once a prescription is dispensed, the product will be labeled with information to assist law enforcement in confirming the legitimacy of the prescription and the patient's legal right to possess low-THC cannabis.	
	La Secretería de Salud had 180 days from 04/28/2017			2009 Ogen memo and 2013 DA General James Cole communicated

Notes	(~12/12/2017) to study the medicinal and therapeutic effects of cannabis before creating the framework for a medical marijuana program infrastructure.			state legal medical marijuana is not a priority. The 2014 Rohrabacher-Farr amendment remains in effect to protect state-legal medical cannabis from enforcement of federal law. *The Agricultural Act of 2014 allows for university and state-level departments of agriculture to cultivate cannabis for research into its industrial potential.* January 4, 2018, U.S. Attorney General Jeff Sessions issued a memo instructing U.S. Attorneys to enforce federal law related to marijuana.
Source(s)	http://www.dof.gob.mx/nota_detalle.php?codigo=5487335&fecha=19/06/2017	https://nmhealth.org/about/mcp/svcs/info/	https://www.dps.texas.gov/RSD/CUP/index.htm	Clarke, R. & Merlin, M. (2013). *Cannabis: Evolution and Ethnobotany.* University of California Press p. 185. ISBN 978-0-520-95457-1. Jump up. DEA (2013). *The DEA Position on Marijuana.* Dea.gov. Retrieved May 16, 2018. https://www.justice.gov/opa/pr/justice-department-issues-memo-marijuana-enforcement

Appendix B

El Paso Top Employer Policies

Top Employer in El Paso, TX	Policy	Source
El Paso Independent School District	El Paso Independent School District is committed to maintaining an alcohol and drug free environment and will not tolerate the use of alcohol and illegal drugs in the workplace and at school-related or school-sanctioned activities on or off school property. Employees who use or are under the influence of alcohol or illegal drugs as defined by the Texas Controlled Substances Act during working hours may be dismissed. The District's policy regarding employee drug use can be found online at www.episd.org. See policies DH (Local) and DI (Local) and (Exhibit). Policy Code: DHE(Local) Policy Title: Employee Standards of Conduct Searches and Alcohol/Drug Testing Action and Summary of Revisions: REVISE POLICY The enclosed revisions are recommended to clarify when REASONABLE SUSPICION ALCOHOL OR DRUG SCREENING is required for an employee. At DRUG-RELATED VIOLATIONS, employees subject to the Department of Transportation testing program would not be eligible for reinstatement if they are found to have a drug-related violation. Approved: YES	http://www.allenrhaynes.com/uploads/2/1/8/6/21865464/episd_employee_handbook_-_20140108.pdf https://tools.episd.org/tools/inline/file_manager/board/policy_manual/MTYsNjcsMTYk0T_opIA0gbqtLbd3oVrtLnUWoMNK-I1ySd3Jx1dRJWMFdEY-bRQx62QIpYvfruVY0hUf_ay1jHvJ9RyyiLby30VFt-RR31ShxgJkYAlg3CcYWvHIplR38x8wEI4972w0W0RA
Fort Bliss	Federal law on marijuana remains unchanged. Marijuana is categorized as a controlled substance under Schedule I of the Controlled Substance Act. Thus knowing or intentional marijuana possession is illegal, even if an individual has no intent to manufacture, distribute, or dispense marijuana. In addition, Executive Order 12564, Drug-Free Federal Workplace, mandates that (a) Federal employees are required to refrain from the use of illegal drugs; (b) the use of illegal drugs by Federal employees, whether on or off duty, is contrary to the efficiency of the service; and (c) persons who use illegal drugs are not suitable for Federal employment. The Executive Order emphasizes, however, that	https://chcoc.gov/content/federal-laws-and-policies-prohibiting-marijuana-use

	discipline is not required for employees who voluntarily seek counseling or rehabilitation and thereafter refrain from using illegal drugs.	
Ysleta Independent School District	Ysleta ISD is committed to maintaining an alcohol and drug-free environment and will not tolerate the use of alcohol and/or illegal drugs in the workplace and at school related or school-sanctioned activities on or off school property. Employees who use or are under the influence of alcohol or illegal drugs as defined by the Texas Controlled Substances Act during work hours may be dismissed. The district's policy regarding employee drug use is as follows: An employee shall not manufacture, distribute, dispense, possess, use, or be under the influence of any of the following substances during or outside of usual working hours: Any controlled substance or dangerous drug defines by law including but not limited to marijuana, any narcotic drug, hallucinogen, stimulant, depressant, amphetamine, or barbiturate. EXCEPTIONS: Sn employee who manufactures, possesses, or dispenses a substance listed above as part of the employee's job responsibilities, or who uses the drug authorized by a licensed physician prescribed for the employee's personal use shall not be considered to have violated this policy.	https://www.yisd.net/cms/lib/TX01917279/Centricity/Domain/498/2017-2018%20Employee%20Handbook.pdf
The University of Texas at El Paso	The unlawful purchase, manufacture, sale, distribution, possession, storage or use of an illegal drug or controlled substance in or on any premises or property owned or controlled by the University is prohibited. All persons who are applicants for or who are employed as Commissioned Police Officers, in positions with duties or activities that require possession of a commercial driver's license, or in certain other safety-sensitive positions, designated by the University, will be required to provide a urine sample for testing for the presence of illegal drugs and/or alcohol.	https://admin.utep.edu/Default.aspx?tabid=30505